



(19)

Europäisches Patentamt
European Patent Office
Office européen des brevets



(11)

EP 0 656 887 B1

(12)

EUROPEAN PATENT SPECIFICATION

(45) Date of publication and mention
of the grant of the patent:
28.10.1998 Bulletin 1998/44

(21) Application number: **93923714.5**

(22) Date of filing: **24.08.1993**

(51) Int Cl.⁶: **C07C 311/29, C07D 213/30,
C07K 5/06, C07C 317/44,
C07C 311/05, C07C 311/18,
C07D 213/89, C07D 215/48,
C07C 317/14, C07D 239/26,
C07D 213/81**

(86) International application number:
PCT/US93/07814

(87) International publication number:
WO 94/04492 (03.03.1994 Gazette 1994/06)

(54) HYDROXYETHYLAMINO SULFONAMIDES USEFUL AS RETROVIRAL PROTEASE INHIBITORS

HYDROXYETHYLAMINOSULFONAMIDE VERWENDBAR ALS INHIBTOREN RETROVIRALER
PROTEASEN

SULFAMIDES D'HYDROXYETHYLAMINO UTILES COMME INHIBITEURS DE PROTEASES
RETROVIRALES

(84) Designated Contracting States:
**AT BE CH DE DK ES FR GB GR IE IT LI LU NL PT
SE**

(30) Priority: **25.08.1992 US 934984**

(43) Date of publication of application:
14.06.1995 Bulletin 1995/24

(60) Divisional application: **97113434.1 / 0 810 209**

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- | | |
|------------------------|------------------------|
| EP-A- 0 264 795 | EP-A- 0 468 641 |
| WO-A-92/08699 | |

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Description**1. Field of the Invention**

5 The present invention relates to retroviral protease inhibitors and, more particularly, relates to novel compounds and a composition and method for inhibiting retroviral proteases. This invention, in particular, relates to sulfonamide-containing hydroxyethylamine protease inhibitor compounds, a composition and method for inhibiting retroviral proteases such as human immunodeficiency virus (HIV) protease and for treating a retroviral infection, e.g., an HIV infection. The subject invention also relates to processes for making such compounds as well as to intermediates useful in
10 such processes.

2. Related Art

15 During the replication cycle of retroviruses, gag and gag-pol gene products are translated as proteins. These proteins are subsequently processed by a virally encoded protease (or proteinase) to yield viral enzymes and structural proteins of the virus core. Most commonly, the gag precursor proteins are processed into the core proteins and the pol precursor proteins are processed into the viral enzymes, e.g., reverse transcriptase and retroviral protease. It has been shown that correct processing of the precursor proteins by the retroviral protease is necessary for assembly of infectious viroids. For example, it has been shown that frameshift mutations in the protease region of the pol gene of HIV prevents
20 processing of the gag precursor protein. It has also been shown through site-directed mutagenesis of an aspartic acid residue in the HIV protease that processing of the gag precursor protein is prevented. Thus, attempts have been made to inhibit viral replication by inhibiting the action of retroviral proteases.

25 Retroviral protease inhibition may involve a transition-state mimetic whereby the retroviral protease is exposed to a mimetic compound which binds to the enzyme in competition with the gag and gag-pol proteins to thereby inhibit replication of structural proteins and, more importantly, the retroviral protease itself. In this manner, retroviral replication proteases can be effectively inhibited.

30 Several classes of compounds have been proposed, particularly for inhibition of proteases, such as for inhibition of HIV protease. Such compounds include hydroxyethylamine isosteres and reduced amide isosteres. See, for example, EP O 346 847; EP O 342,541; Roberts et al, "Rational Design of Peptide-Based Proteinase Inhibitors," *Science*, 248, 358 (1990); and Erickson et al, "Design Activity, and 2.8 \AA Crystal Structure of a C₂ Symmetric Inhibitor Complexed to HIV-1 Protease," *Science*, 249, 527 (1990).

35 Several classes of compounds are known to be useful as inhibitors of the proteolytic enzyme renin. See, for example, U.S. No. 4,599,198; U.K. 2,184,730; G.B. 2,209,752; EP O 264 795; G.B. 2,200,115 and U.S. SIR H725. Of these, G.B. 2,200,115, GB 2,209,752, EP O 264,795, U.S. SIR H725 and U.S. 4,599,198 disclose urea-containing hydroxyethylamine renin inhibitors. G.B. 2,200,115 also discloses sulfamoyl-containing hydroxyethylamine renin inhibitors, and EP 0264 795 discloses certain sulfonamide-containing hydroxyethylamine renin inhibitors. However, it is known that, although renin and HIV proteases are both classified as aspartyl proteases, compounds which are effective renin inhibitors generally cannot be predicted to be effective HIV protease inhibitors.

40 The EP-A 0 468 641 discloses 2S-hydroxy-substituted dipeptide carbonyl as well as sulfonamide derivatives which are useful as renin inhibitors.

BRIEF DESCRIPTION OF THE INVENTION

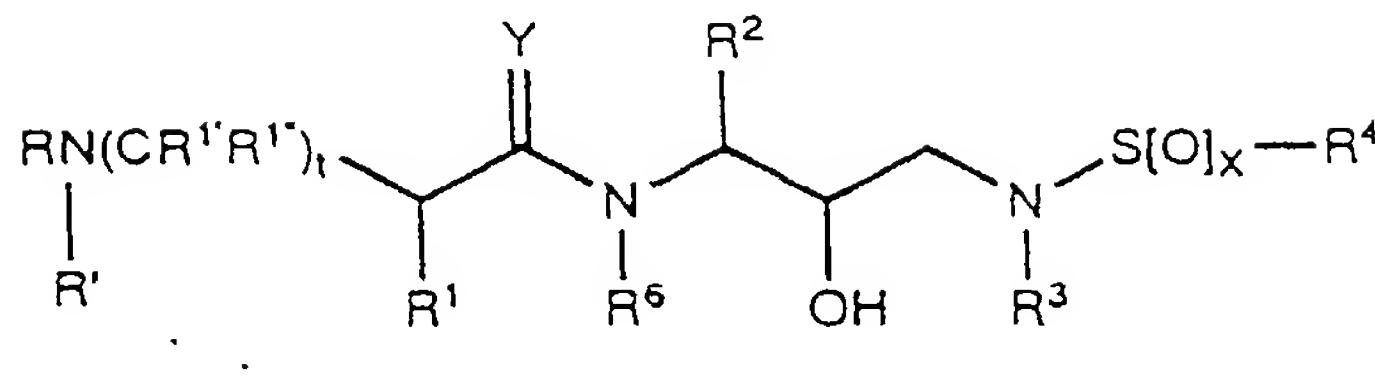
45 The present invention is directed to virus inhibiting compounds and compositions. More particularly, the present invention is directed to retroviral protease inhibiting compounds and compositions, to the use of such compounds for preparing medicaments for inhibiting proteases, especially for inhibiting HIV protease and for treating a retroviral infection such as HIV infection and for treating AIDS, to processes for preparing the compounds and to intermediates useful in such processes. The subject compounds are characterized as sulfonamide-containing hydroxyethylamine inhibitor compounds.

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DETAILED DESCRIPTION OF THE INVENTION

In accordance with the present invention, there is provided a retroviral protease inhibiting compound of the formula:

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10 or a pharmaceutically acceptable salt, prodrug or ester thereof wherein:

R represents hydrogen, alkoxycarbonyl, aralkoxycarbonyl, alkylcarbonyl, cycloalkylcarbonyl, cycloalkylalkoxycarbonyl, cycloalkylalkanoyl, alkanoyl, aralkanoyl, aroyl, aryloxycarbonyl, aryloxycarbonylalkyl, aryloxyalkanoyl, heterocyclcarbonyl, heterocycloxycarbonyl, heterocyclalkanoyl, heterocyclalkoxycarbonyl, heteroaralkanoyl, heteroaralkoxycarbonyl, heteroaryloxycarbonyl, heteroaroyl, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, aralkyl, aryloxyalkyl, heteroaryloxyalkyl, hydroxyalkyl, aminocarbonyl, aminoalkanoyl, and mono- and disubstituted aminocarbonyl and mono- and disubstituted aminoalkanoyl radicals wherein the substituents are selected from alkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroaralkyl, heterocycloalkyl, heterocycloalkylalkyl radicals, or where said aminocarbonyl and aminoalkanoyl radicals are disubstituted, said substituents along with the nitrogen atom to which they are attached form a heterocycloalkyl or heteroaryl radical;

R' represents hydrogen, radicals as defined for R³ or R"SO₂⁻ wherein R" represents radicals as defined for R³; or R and R' together with the nitrogen to which they are attached represent heterocycloalkyl and heteroaryl radicals;

25 R¹ represents hydrogen, -CH₂SO₂NH₂, -CH₂CO₂CH₃, -CO₂CH₃, -CONH₂, -CH₂C(O)NHCH₃, -C(CH₃)₂(SH), -C(CH₃)₂(SCH₃), -C(CH₃)₂(S[O]CH₃), -C(CH₃)₂(S[O]₂CH₃), alkyl, haloalkyl, alkenyl, alkynyl and cycloalkyl radicals, and amino acid side chains selected from asparagine, S-methyl cysteine and the sulfoxide (SO) and sulfone (SO₂) derivatives thereof, isoleucine, allo-isoleucine, alanine, leucine, tert-leucine, phenylalanine, ornithine, histidine, norleucine, glutamine, threonine, glycine, allothreonine, serine, O-alkyl serine, aspartic acid, beta-cyano alanine and valine side chains;

30 R^{1'} and R^{1''} independently represent hydrogen and radical as defined for R¹; or one of R^{1'} and R^{1''}, together w/ R¹ and the carbon atoms to which R^{1'}, R^{1''} and R¹ are attached, represent a cycloalkyl radical;

35 R² represents alkyl, aryl, cycloalkyl, cycloalkylalkyl and aralkyl radicals, which radicals are optionally substituted with a group selected from alkyl and halogen radicals, -NO₂, -CN, -CF₃, -OR⁹ and -SR⁹, wherein R⁹ represents hydrogen and alkyl radicals, and halogen radicals;

40 R³ represents hydrogen, alkyl, haloalkyl, alkenyl, alkynyl, hydroxyalkyl, alkoxyalkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heteroaryl, heterocycloalkylalkyl, aryl, aralkyl, heteroaralkyl, aminoalkyl and mono- and disubstituted aminoalkyl radicals, wherein said substituents are selected from alkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroaralkyl, heterocycloalkyl, and heterocycloalkylalkyl radicals, or in the case of a disubstituted aminoalkyl radical, said substituents along with the nitrogen atom to which they are attached, form a heterocycloalkyl or a heteroaryl radical;

45 R⁴ represents radicals as defined by R³ except for hydrogen;

R⁶ represents hydrogen and alkyl radicals;

50 x represents 0, 1 or 2;

t represents either 0 or 1; and

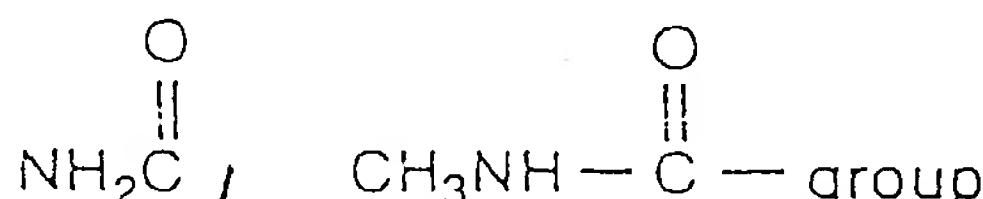
55 Y represents O, S and NR¹⁵ wherein R¹⁵ represents hydrogen and radicals as defined for R³.

A family of compounds of particular interest within Formula I are compounds wherein t is 0, Y is O, x is 2, R⁶ = hydrogen and with R' as defined above except R" SO₂, with R¹ as defined above except O-alkylserine being replaced by O-methylserine, with R³ as above except hydrogen, with R, R² and R⁴ as defined above.

Preferred compounds of the above group are those wherein R represents aralkoxycarbonyl and heteroaroyl radicals; or wherein R represents carbobenzoxy, 2-benzofurancarbonyl and 2-quinolinylcarbonyl radicals; or wherein R¹ represents alkyl, alkynyl and alkenyl radicals, and amino acid side chains selected from the group consisting of asparagine, valine, threonine, allo-threonine, isoleucine, S-methyl cysteine and the sulfone and sulfoxide derivatives thereof, alanine, and allo-isoleucine; or wherein R¹ represents methyl, propargyl, t-butyl, isopropyl and sec-butyl radicals, and amino acid side chains selected from the group consisting of asparagine, valine, S-methyl cysteine, allo-iso-leucine, iso-leucine, threonine, serine, aspartic acid, beta-cyano alanine, and allo-threonine side chains; or wherein R¹ represents propargyl and t-butyl radicals; or wherein R⁴ represents phenyl and substituted phenyl radicals and wherein R³ represents n-pentyl, n-hexyl, n-propyl, i-butyl, cyclohexyl, neo-pentyl, i-amyl, and n-butyl radicals; or wherein R³ and R⁴ independently represent alkyl radicals having from 2 to 5 carbon atoms, cycloalkylalkyl radicals, aralkyl radicals, heterocycloalkylalkyl radicals or heteroaralkyl radicals; or wherein R³ represents isobutyl, n-propyl, n-butyl, isoamyl, cyclohexyl, cyclohexylmethyl radicals and R⁴ represents phenyl and substituted phenyl radicals; or wherein R³ is i-amyl or i-butyl and R⁴ is phenyl or substituted phenyl selected from para-chlorophenyl, para-fluorophenyl, para-nitrophenyl, para-aminophenyl, and para-methoxyphenyl; or wherein R⁴ represents heteroaryl radicals; or wherein R³ is a p-fluorobenzyl radical and R⁴ is a phenyl radical or substituted phenyl selected from para-chlorophenyl, para-fluorophenyl, para-nitrophenyl, para-aminophenyl and para-methoxyphenyl; or wherein R³ is a 4-pyridylmethyl radical or its N-oxide and R⁴ is a phenyl radical or substituted phenyl selected from para-chlorophenyl, para-fluorophenyl, para-nitrophenyl, para-aminophenyl, and para-methoxyphenyl; or wherein R⁴ represents an alkyl radical having from 1 to 6 carbon atoms or a 5 or 6-membered heterocycl radical, optionally substituted with an alkyl radical having from 1 to 3 carbon atoms; or wherein R¹ and R¹" are both hydrogen and R¹ represents -CH₂SO₂NH₂, CO₂NH₂, CO₂CH₃, alkyl and cycloalkyl radicals and amino acid side chains selected from asparagine, S-methyl cysteine and the sulfone and sulfoxide derivatives thereof, histidine, norleucine, glutamine, glycine, allo-isoleucine, alanine, threonine, isoleucine, leucine, tert-leucine, phenylalanine, ornithine, allo-threonine, serine, aspartic acid, beta-cyano alanine and valine side chains; Or wherein R¹ represents the amino acid side chain of asparagine and R represents heteroaroyl radical; or wherein R¹ represents a t-butyl or a propargyl radical or an amino acid side chain of valine or isoleucine; or above compounds where R represents an arylalkanoyl, aryloxycarbonyl, alkanoyl, aminocarbonyl, mono-substituted aminoalkanoyl, or disubstituted aminoalkanoyl, or mono- or dialkylaminocarbonyl radicals; or where R represents acetyl, N,N-dimethylaminoacetyl, N-methylaminoacetyl or N-benzyl-N-methylaminoacetyl; or compounds of formula I where R¹ is a methyl radical; or wherein furthermore R represents an alkanoyl, arylalkanoyl, aryloxyalkanoyl or arylalkyloxylcarbonyl radical; or where R represents a phenoxyacetyl, 2-naphthyloxyacetyl, benzyloxycarbonyl or p-methoxybenzyloxycarbonyl radical; or wherein R represents an N,N-dialkylaminocarbonyl radical; or wherein R represents an aminocarbonyl or an alkylaminocarbonyl radical; or where R represents an N-methylaminocarbonyl radical.

A further group of preferred compounds are those within formula I wherein t = 1, R¹' and R¹" are hydrogen, x is 2, Y is O, R⁶ is hydrogen and wherein R, R², R³, R⁴ are as defined for formula I above and R¹ is as above except O-alkylserine and R' is as above except R" SO₂.

Preferred compounds of that group are those wherein R¹ represents alkyl radicals having from 1 to 4 carbon atoms and alkynyl radicals having from 3 to 8 carbon atoms; or wherein R¹ represents methyl, ethyl, isopropyl, propargyl and t-butyl radicals; or wherein R' is hydrogen and R is



acetyl, phenoxyacetyl, 2-naphthyloxy-carbonyl, benzyloxycarbonyl or p-methoxybenzyloxycarbonyl; or wherein R' is hydrogen and R is an aralkoxycarbonyl radical or a heteroaralkoxycarbonyl radical; or wherein R and R' are independently selected from methyl and phenethyl radicals; or wherein R³ represents alkyl radicals having from 2 to 5 carbon atoms and R⁴ represents methyl, phenyl and substituted phenyl radicals; or wherein R³ represents isobutyl, n-propyl, n-butyl, isoamyl, cyclohexylmethyl, cyclohexyl, benzyl, para-fluorobenzyl, para-methoxybenzyl, para-methylbenzyl and 2-naphthylmethyl radicals and R⁴ represents phenyl and substituted phenyl radicals wherein substituents of the substituted phenyl radical are selected from chloro, fluoro, nitro, methoxy and amino substituents; or wherein R³ is cyclohexylmethyl and R⁴ phenyl, or R³ is i-amyl and R⁴ is phenyl, or R³ is i-butyl and R⁴ is phenyl, or R³ is n-butyl and R⁴ is phenyl, or R³ is cyclohexyl and R⁴ is phenyl; or wherein R⁴ represents methyl and cyclohexyl radicals; or wherein R and R' together with the nitrogen to which they are bonded represent pyrrolidinyl, piperidinyl, morpholinyl, and piperazinyl radicals; or wherein R³ represents heteroaralkyl radicals and R⁴ is methyl or phenyl.

Another group of preferred compounds within formula I are those wherein t = 1, x = 2, Y is O, R⁶ is hydrogen and

wherein R, R¹, R^{1'}, R², R⁴ are as defined for formula I above and wherein R³ is as above 1 except hydrogen and R¹ is as for formula I except O-alkylserine and wherein R' is as for formula I except R" SO₂.

Preferred compounds of that group are those wherein R' represents hydrogen and R represents aralkoxycarbonyl and heteroaroyl radicals; or wherein R' is hydrogen and R represents carbobenzoxy, 2-benzofurancarbonyl, and 2-quinolinylcarbonyl radicals; or wherein R¹, R^{1'} and R^{1''} independently represent hydrogen and alkyl radicals having from 1 to about 4 carbon atoms, alkenyl, alkynyl, aralkyl radicals and radicals selected from -CH₂SO₂NH₂, -CO₂CH₃, -CONHCH₃, -CON(CH₃)₂, -CH₂C(O)NHCH₃, -CH₂C(O)N(CH₃)₂, -CONH₂, -C(CH₃)₂(SCH₃), -C(CH₃)₂(S[O]CH₃); or wherein R¹, R^{1'} and R^{1''} independently represent hydrogen, methyl, ethyl, benzyl, phenylpropyl, propargyl, hydroxyl and radicals selected from -C(O)OCH₃, -C(O)NH₂, -C(O)OH; or wherein R¹ and R^{1'} are both hydrogen and R^{1''} is C(O)NH₂; or wherein R¹ and R^{1'} are both hydrogen and R^{1''} is methyl; or wherein R^{1'} is hydrogen and R¹ and R^{1''} together with the carbon atoms to which they are attached form a three to six-membered cycloalkyl radical; or wherein R is carbobenzoxy, 2-quinolinylcarbonyl and 2-benzofuran carbonyl radicals; or wherein R³ represents alkyl radicals having from 2 to 5 carbon atoms; or wherein R³ independently represent n-propyl, i-butyl, cyclohexyl, cyclohexylmethyl, i-amyl and n-butyl radicals and R⁴ represents phenyl and substituted phenyl radicals or wherein R³ and R⁴ independently represent alkyl radicals having from 2 to 5 carbon atoms, cycloalkylalkyl radicals, aryl radicals, heteroaryl radicals, aralkyl radicals, heterocycloalkylalkyl radicals and heteroaralkyl radicals; or wherein R³ represents benzyl, para-fluorobenzyl, para-methoxybenzyl, para-methylbenzyl, and 2-naphthylmethyl radicals and R⁴ represents phenyl and substituted phenyl radicals wherein substituents of the substituted phenyl radical are selected from chloro fluoro, nitro, methoxy and amino substituents.

Especially preferred compounds of the above groups of interest within formula I are those wherein R² represents alkyl, cycloalkylalkyl radicals, which radicals are optionally substituted with halogen radicals and radicals represented by the formula -OR⁹ and -SR⁹ wherein R⁹ represents hydrogen and alkyl radicals; or wherein R² represents CH₃SCH₂CH₂- isobutyl, n-butyl, benzyl, 2-naphthylmethyl and cyclohexylmethyl radicals; or wherein R³ and R⁴ independently represent alkyl, haloalkyl, alkenyl, alkoxyalkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl, aryl, aralkyl and heteroaralkyl radicals; or wherein R³ represents alkyl and alkenyl radicals and R⁴ represents aryl radicals.

Specific compounds within Formula I are the following:

Phenylmethyl[2R-hydroxy-3-[(3-methylbutyl)(methylsulfonyl)amino]-1S-(phenylmethyl)propyl]carbamate;

Phenylmethyl[2R-hydroxy-3-[(3-methylbutyl)(phenylsulfonyl)amino]-1S-(phenylmethyl)propyl]carbamate;

N1-[2R-hydroxy-3-[(3-methylbutyl)(methylsulfonyl)amino]-1S-(phenylmethyl)propyl]-2S-[(2-quinolinylcarbonyl)amino]butanediamide;

N1-[2R-hydroxy-3-[(3-methylbutyl)(methylsulfonyl)amino]-1S-(phenylmethyl)propyl]-2S-[(phenylmethyloxycarbonyl)amino]butanediamide;

N1-[2R-hydroxy-3-[(3-methylbutyl)(phenylsulfonyl)amino]-1S-(phenylmethyl)propyl]-2S-[(2-quinolinylcarbonyl)amino]butanediamide;

N1-[2R-hydroxy-3-[(3-methylbutyl)(phenylsulfonyl)amino]-1S-(phenylmethyl)propyl]-2S-[(phenylmethyloxycarbonyl)amino]butanediamide;

2S-[(dimethylamino)acetyl]amino]-N-[2R-hydroxy-3-[(3-methylbutyl)(phenylsulfonyl)amino]-1S-(phenylmethyl)propyl]-3,3-dimethylbutaneamide;

2S-[(methylamino)acetyl]amino]-N-2R-hydroxy-3-[(3-methylbutyl)(phenylsulfonyl)amino]-1S-(phenylmethyl)propyl]-3,3-dimethylbutaneamide; or

N1-[2R-hydroxy-3-[(3-methylbutyl)(phenylsulfonyl)amino]-N4-methyl-1S-(phenylmethyl)propyl]-2S-[(2-quinolinylcarbonyl)amino]butanediamide; or

[3-[[2-hydroxy-3-((3-methylbutyl)(phenylsulfonyl)amino)-1-(phenylmethyl)propyl]amino]-2-methyl-3-oxopropyl]-, (4-methoxyphenyl)methyl ester, [1S-[1R*(S*),2S*]]-.

As utilized herein, the term "alkyl", alone or in combination, means a straight-chain or branched-chain alkyl radical containing from 1 to 10, preferably from 1 to 8, carbon atoms. Examples of such radicals include methyl, ethyl, n-propyl,

isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isoamyl, hexyl, or octyl. The term "alkenyl", alone or in combination, means a straight-chain or branched-chain hydrocarbon radical having one or more double bonds and containing from 2 to 18 carbon atoms preferably from 2 to 16 carbon atoms. Examples of suitable alkenyl radicals include ethenyl, propenyl), alkyl, 1,4-butadienyl. The term "alkynyl", alone or in combination, means a straight-chain hydrocarbon radical having one or more triple bonds and containing from 2 to 10 carbon atoms. Examples of alkynyl radicals include ethynyl, propynyl, (propargyl) or butynyl. The term "alkoxy", alone or in combination, means an alkyl ether radical wherein the term alkyl is as defined above. Examples of suitable alkyl ether radicals include methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, iso-butoxy, sec-butoxy, or tert-butoxy. The term "cycloalkyl", alone or in combination, means a saturated or partially saturated monocyclic, bicyclic or tricyclic alkyl radical wherein each cyclic moiety contains from 3 to 8 carbon atoms and is cyclic. The term "cycloalkylalkyl" means an alkyl radical as defined above which is substituted by a cycloalkyl radical containing from 3 to 8, preferably from 3 to 6, carbon atoms. Examples of such cycloalkyl radicals include cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl.

The term "aryl", alone or in combination, means a phenyl or naphthyl radical which optionally carries one or more substituents selected from alkyl, alkoxy, halogen, hydroxy, amino, nitro, cyano, haloalkyl and the like, such as phenyl, p-tolyl, 4-methoxyphenyl, 4-(tert-butoxy)phenyl, 4-fluorophenyl, 4-chlorophenyl, 4-hydroxyphenyl, 1-naphthyl, or 2-naphthyl. The term "aralkyl", alone or in combination, means an alkyl radical as defined above in which one hydrogen atom is replaced by an aryl radical as defined above, such as benzyl, or 2-phenylethyl. The term "aralkoxy carbonyl", alone or in combination, means a radical of the formula -C(O)-O-aralkyl in which the term "aralkyl" has the significance given above. An example of an aralkoxycarbonyl radical is benzyloxycarbonyl. The term "aryloxy" means a radical of the formula aryl-O- in which the term aryl has the significance given above. The term "alkanoyl", alone or in combination, means an acyl radical derived from an alkanecarboxylic acid, examples of which include acetyl, propionyl, butyryl, valeryl, or 4-methylvaleryl. The term "cycloalkylcarbonyl" means an acyl group derived from a monocyclic or bridged cycloalkanecarboxylic acid such as cyclopropanecarbonyl, cyclohexanecarbonyl, or adamantanecarbonyl, or from a benz-fused monocyclic cycloalkanecarboxylic acid which is optionally substituted by, for example, alkanoylamino, such as 1,2,3,4-tetrahydro-2-naphthoyl,2-acetamido-1,2,3,4-tetrahydro-2-naphthoyl. The term "aralkanoyl" means an acyl radical derived from an aryl-substituted alkanecarboxylic acid such as phenylacetyl, 3-phenylpropionyl (hydrocinnamoyl), 4-phenylbutyryl, (2-naphthyl)acetyl, 4-chlorohydrocinnamoyl, 4-aminohydrocinnamoyl, or 4-methoxyhydrocinnamoyl.

The term "aroyl" means an acyl radical derived from an aromatic carboxylic acid. Examples of such radicals include aromatic carboxylic acids, an optionally substituted benzoic or naphthoic acid such as benzoyl, 4-chlorobenzoyl, 4-carboxybenzoyl, 4-(benzyloxycarbonyl)benzoyl, 1-naphthoyl, 2-naphthoyl, 6-carboxy-2 naphthoyl, 6-(benzyloxycarbonyl)-2-naphthoyl, 3-benzyloxy-2-naphthoyl, 3-hydroxy-2-naphthoyl, or 3-(benzyloxyformamido)-2-naphthoyl. The heterocycl or heterocycloalkyl portion of a heterocyclcarbonyl, heterocyclloxycarbonyl, hecerocyclalkoxycarbonyl, or heterocyclalkyl group is a saturated or partially unsaturated monocyclic, bicyclic or tricyclic heterocycle which contains one or more hetero atoms selected from nitrogen, oxygen and sulphur, which is optionally substituted on one or more carbon atoms by halogen, alkyl, alkoxy, oxo, and the like, and/or on a secondary nitrogen atom (i.e., -NH-) by alkyl, aralkoxycarbonyl, alkanoyl, phenyl or phenylalkyl or on a tertiary nitrogen atom (i.e. = N-) by oxido and which is attached via a carbon atom. The heteroaryl portion of a heteroaroyl, heteroaryloxycarbonyl, or a heteroaralkoxy carbonyl group is an aromatic monocyclic, bicyclic, or tricyclic heterocycle which contains the hetero atoms and is optionally substituted as defined above with respect to the definition of hecerocycl. Examples of such heterocycl and heteroaryl groups are pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, thiamorpholinyl, pyrrolyl, imidazolyl (e.g., imidazol 4-yl, 1-benzyloxycarbonylimidazol-4-yl, etc.), pyrazolyl, pyridyl, pyrazinyl, pyrimidinyl, furyl, thienyl, triazolyl, oxazolyl, thiazolyl, indolyl (e.g., 2-indolyl, etc.), quinolinyl, (e.g., 2-quinolinyl, 3-quinolinyl, 1-oxido-2-quinolinyl, etc.), isoquinolinyl (e.g., 1-isoquinolinyl, 3-isoquinolinyl, etc.), tetrahydroquinolinyl (e.g., 1,2,3,4-tetrahydro-2-quinolyl, etc.), 1,2;3,4-tetrahydroisoquinolinyl (e.g., 1,2,3,4-tetrahydro-1-oxo-isoquinolinyl, etc.), quinoxalinyl, β-carbolinyl, 2-benzofurancarbonyl, 1-, 2-,4- or 5-benzimidazolyl. The term "cycloalkylalkoxycarbonyl" means an acyl group derived from a cycloalkylalkoxycarboxylic acid of the formula cycloalkylalkyl-O-COOH wherein cycloalkylalkyl has the significance given above. The term "aryloxyalkanoyl" means an acyl radical of the formula aryl-O-alkanoyl wherein aryl and alkanoyl have the significance given above. The term "heterocyclloxycarbonyl" means an acyl group derived from heterocycl-O-COOH wherein heterocycl is as defined above. The term "heterocyclalkanoyl" is an acyl radical derived from a heterocycl-substituted alkane carboxylic acid wherein heterocycl has the significance given above. The term "heterocyclalkoxycarbonyl" means an acyl radical derived from a heterocycl-substituted alkane-O-COOH wherein heterocycl has the significance given above. The term "heteroaryloxycarbonyl" means an acyl radical derived from a carboxylic acid represented by heteroaryl-O-COOH wherein heteroaryl has the significance given above. The term "aminocarbonyl" alone or in combination, means an amino-substituted carbonyl (carbamoyl) group derived from an amino-substituted carboxylic acid wherein the amino group can be a primary, secondary or tertiary amino group containing substituents selected from hydrogen, and alkyl, aryl, aralkyl, cycloalkyl, or cycloalkylalkyl radicals. The term "aminoalkanoyl" means an acyl group derived from an amino-substituted alkanecarboxylic acid wherein the amino group can be a primary,

secondary or tertiary amino group containing substituents selected from hydrogen, and alkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl or radicals. The term "halogen" means fluorine, chlorine, bromine or iodine. The term "haloalkyl" means an alkyl radical having the significance as defined above wherein one or more hydrogens are replaced with a halogen. Examples of such haloalkyl radicals include chloromethyl, 1-bromoethyl, fluoromethyl, difluoromethyl, trifluoromethyl, or 1,1,1-trifluoroethyl. The term "leaving group" generally refers to groups readily displaceable by a nucleophile, such as an amine, a thiol or an alcohol nucleophile. Such leaving groups are well known in the art. Examples of such leaving groups include, but are not limited to, N-hydroxysuccinimide, N-hydroxybenzotriazole, halides, triflates, or tosylates.

Preferred leaving groups are indicated herein where appropriate.

Procedures for preparing the compounds of Formula I are set forth below. It should be noted that the general procedure is shown as it relates to preparation of compounds having the specified stereochemistry, for example, wherein the absolute stereochemistry about the hydroxyl group is designated as (R). However, such procedures are generally applicable to those compounds of opposite configuration, e.g., where the stereochemistry about the hydroxyl group is (S). In addition, the compounds having the (R) stereochemistry can be utilized to produce those having the (S) stereochemistry. For example, a compound having the (R) stereochemistry can be inverted to the (S) stereochemistry using well-known methods.

Preparation of Compounds of Formula I

The compounds of the present invention represented by Formula I above can be prepared utilizing the following general procedure. This procedure is schematically shown in the following Schemes I and II:

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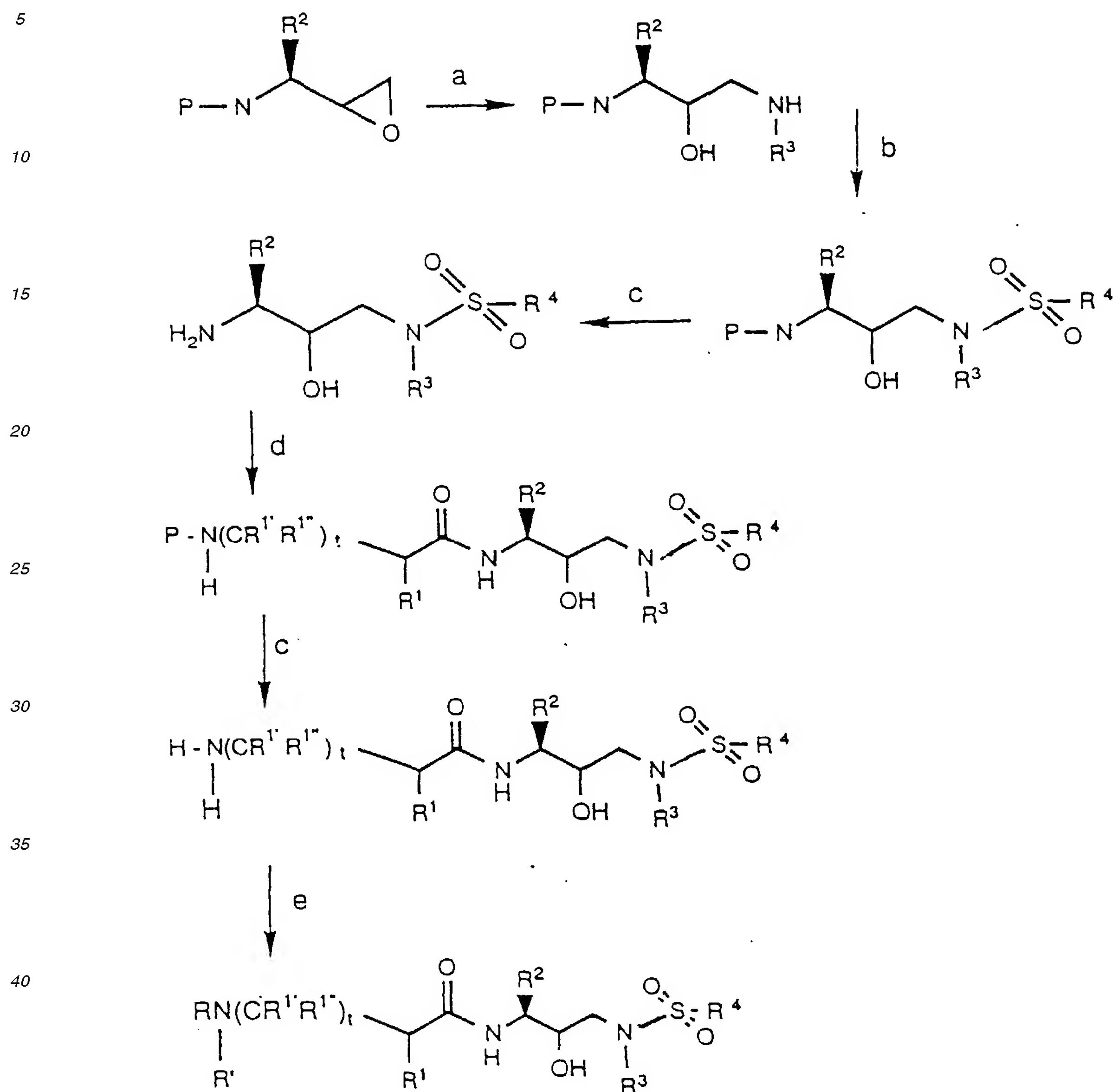
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SCHEME I

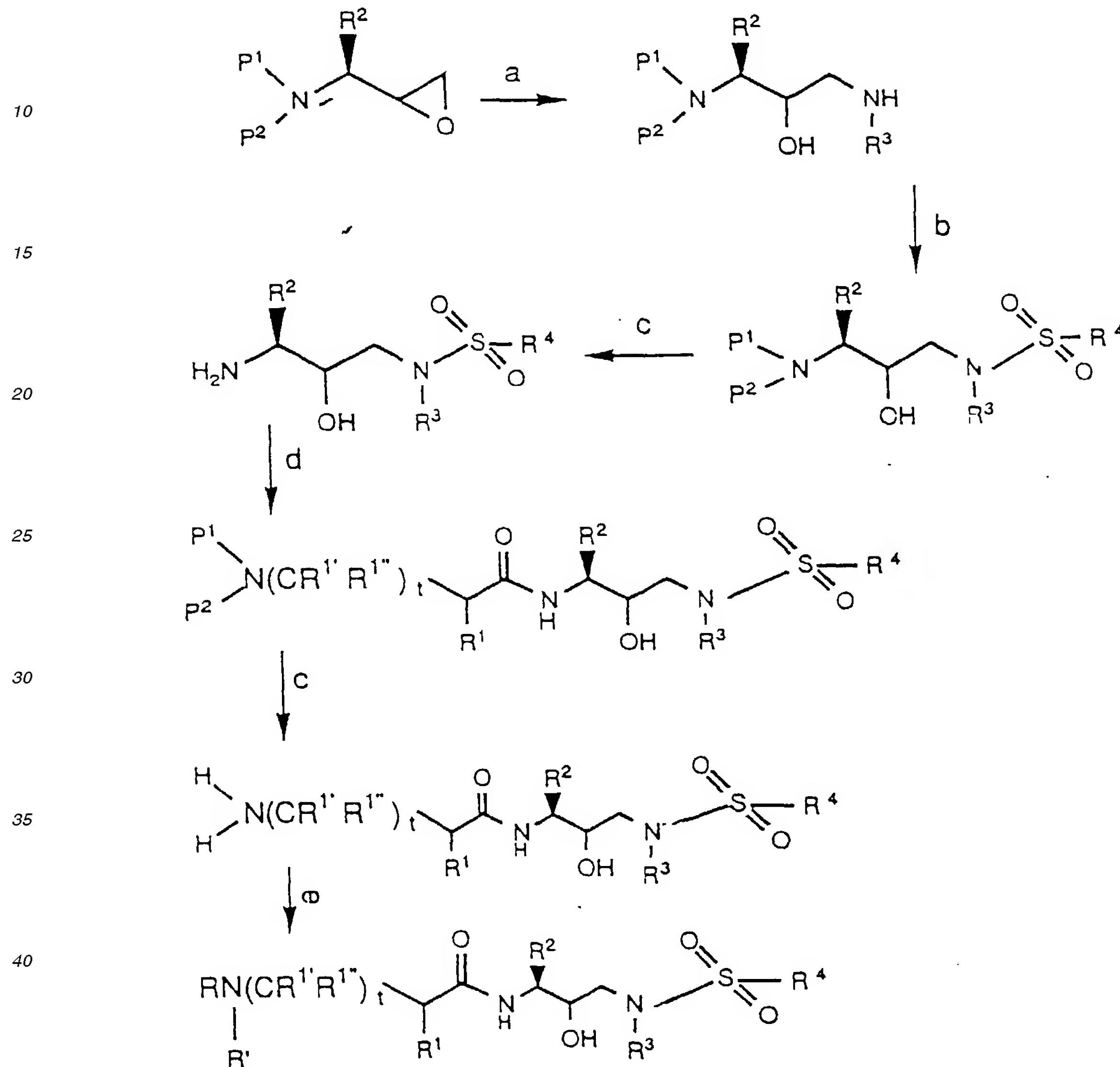
a) amine b) sulfonyl chloride R^4SO_2Cl (or anhydride) + acid scavenger c) deprotection d) coupling e) coupling.

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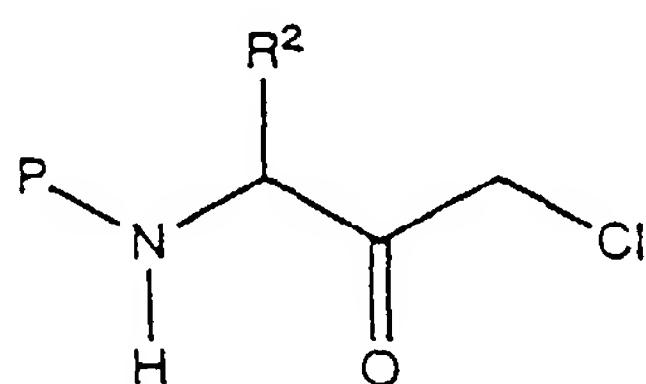
SCHEME II

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a) amine b) sulfonyl chloride R^4SO_2Cl (or anhydride) + acid scavenger c) deprotection d) coupling e) coupling.
An N-protected chloroketone derivative of an amino acid having the formula:

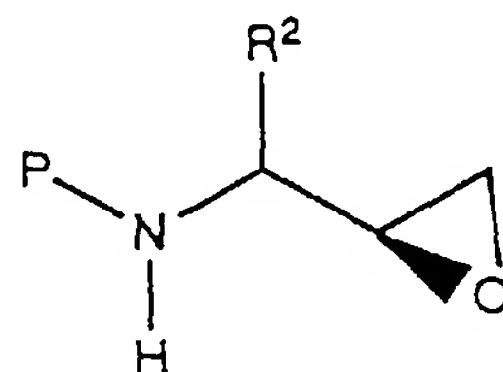
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wherein P represents an amino protecting group, and R² is as defined above, is reduced to the corresponding alcohol

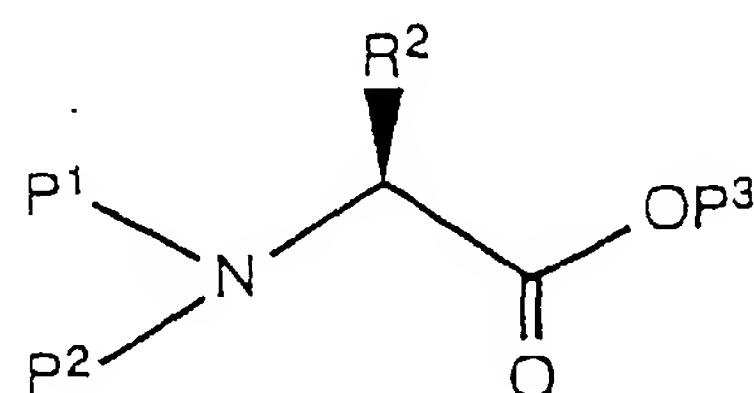
utilizing an appropriate reducing agent. Suitable amino protecting groups are well known in the art and include carbobenzoxy, or t-butoxycarbonyl. A preferred amino protecting group is carbobenzoxy. A preferred N-protected chloroketone is N-benzyloxycarbonyl-L-phenylalanine chloromethyl ketone. A preferred reducing agent is sodium borohydride. The reduction reaction is conducted at a temperature of from -10°C to about 25°C, preferably at about 0°C, in a suitable solvent system such as, for example, tetrahydrofuran. The N-protected chloroketones are commercially available, e.g., such as from Bachem, Inc., Torrance, California. Alternatively, the chloroketones can be prepared by the procedure set forth in S. J. Fittkau, *J. Prakt. Chem.*, 315, 1037 (1973), and subsequently N-protected utilizing procedures which are well known in the art.

The halo alcohol can be utilized directly, as described below, or, preferably, is then reacted, preferably at room temperature, with a suitable base in a suitable solvent system to produce an N-protected amino epoxide of the formula:



wherein P and R² are as defined above. Suitable solvent systems for preparing the amino epoxide include ethanol, methanol, isopropanol, tetrahydrofuran, dioxane, and the like including mixtures thereof. Suitable bases for producing the epoxide from the reduced chloroketone include potassium hydroxide, sodium hydroxide, potassium t-butoxide, or DBU. A preferred base is potassium hydroxide.

Alternatively, a protected amino epoxide can be prepared, such as in co-owned and co-pending PCT Patent Application Serial No. PCT/US93/04804 whcih is incorporated herein by reference, starting with an L-amino acid which is reacted with a suitable amino-protecting group in a suitable solvent to produce an amino-protected L-amino acid ester of the formula:



wherein P³ represents carboxyl-protecting group, e.g., methyl, ethyl, benzyl, or tertiary-butyl.; R² is as defined above; and P¹ and P² independently are selected from amine protecting groups, including but not limited to, arylalkyl, substituted arylalkyl, cycloalkenylalkyl and substituted cycloalkenylalkyl, allyl, substituted allyl, acyl, alkoxy carbonyl, aralkoxy carbonyl and silyl. Examples of arylalkyl include, but are not limited to benzyl, orthomethylbenzyl, trityl and benzhydryl, which can be optionally substituted with halogen, alkyl of C₁-C₈, alkoxy, hydroxy, nitro, alkylene, amino, alkylamino, acylamino and acyl, or their salts, such as phosphonium and ammonium salts. Examples of aryl groups include phenyl, naphthalenyl, indanyl, anthracenyl, durenyl, 9-(9-phenylfluorenyl) and phenanthrenyl, cycloalkenylalkyl or substituted cycloalkenylalkyl radicals containing cycloalkyls of C₆-C₁₀. Suitable acyl groups include carbobenzoxy, t-butoxycarbonyl, iso-butoxycarbonyl, benzoyl, substituted benzoyl, butyryl, acetyl, tri-fluoroacetyl, trichloroacetyl, or phthaloyl.

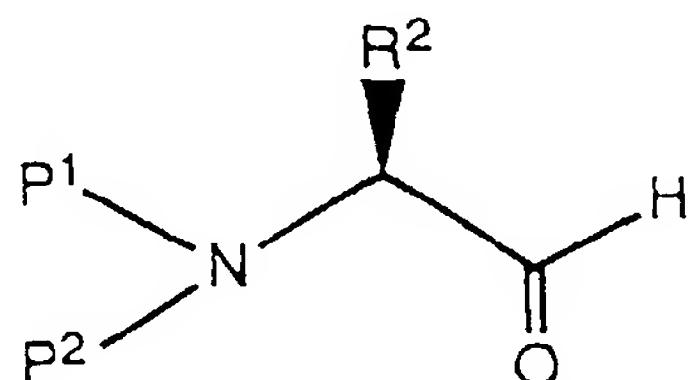
Additionally, the P¹ and/or P² protecting groups can form a heterocyclic ring with the nitrogen to which they are attached, for example, 1,2-bis(methylene)benzene, phthalimidyl, succinimidyl, maleimidyl and the like and where these heterocyclic groups can further include adjoining aryl and cycloalkyl rings. In addition, the heterocyclic groups can be mono-, di- or tri-substituted, e.g., nitrophthalimidyl. The term silyl refers to a silicon atom optionally substituted by one or more alkyl, aryl and aralkyl groups.

Suitable silyl protecting groups include, but are not limited to, trimethylsilyl, triethylsilyl, tri-isopropylsilyl, tert-butyldimethylsilyl, dimethylphenylsilyl, 1,2-bis(dimethylsilyl)benzene, 1,2-bis(dimethylsilyl)ethane and diphenylmethylsilyl. Silylation of the amine functions to provide mono- or bisdisilylamine can provide derivatives of the aminoalcohol, amino acid, amino acid esters and amino acid amide. In the case of amino acids, amino acid esters and amino acid amides, reduction of the carbonyl function provides the required mono- or bis-silyl aminoalcohol. Silylation of the aminoalcohol can lead to the N,N,O-tri-silyl derivative. Removal of the silyl function from the silyl ether function is readily accomplished

by treatment with, for example, a metal hydroxide or ammonium fluoride reagent, either as a discrete reaction step or in situ during the preparation of the amino aldehyde reagent. Suitable silylating agents are, for example, trimethylsilyl chloride, tert-butyl-dimethylsilyl chloride, phenyldimethylsilyl chloride, diphenylmethylsilyl chloride or their combination products with imidazole or DMF. Methods for silylation of amines and removal of silyl protecting groups are well known to those skilled in the art. Methods of preparation of these amine derivatives from corresponding amino acids, amino acid amides or amino acid esters are also well known to those skilled in the art of organic chemistry including amino acid/amino acid ester or aminoalcohol chemistry.

Preferably P¹ and P² are independently selected from aralkyl and substituted aralkyl. More preferably, each of P¹ and P² is benzyl.

The amino-protected L-amino acid ester is then reduced, to the corresponding alcohol. For example, the amino-protected L-amino acid ester can be reduced with diisobutylaluminum hydride at -78° C in a suitable solvent such as toluene. Preferred reducing agents include lithium aluminium hydride, lithium borohydride, sodium borohydride, borane, lithium tri-terbutoxyaluminum hydride, borane/THF complex. Most preferably, the reducing agent is diisobutylaluminum hydride (DiBAL-H) in toluene. The resulting alcohol is then converted, for example, by way of a Swern oxidation, to the corresponding aldehyde of the formula:



wherein P¹, P² and R² are as defined above. Thus, a dichloromethane solution of the alcohol is added to a cooled (-75 to -68° C) solution of oxalyl chloride in dichloromethane and DMSO in dichloromethane and stirred for 35 minutes.

Acceptable oxidizing reagents include, for example, sulfur trioxide-pyridine complex and DMSO, oxalyl chloride and DMSO, acetyl chloride or anhydride and DMSO, trifluoroacetyl chloride or anhydride and DMSO, methanesulfonyl chloride and DMSO or tetrahydrothiophene-S-oxide, toluenesulfonyl bromide and DMSO, trifluoromethanesulfonyl anhydride (triflic anhydride) and DMSO, phosphorus pentachloride and DMSO, dimethylphosphoryl chloride and DMSO and isobutylchloroformate and DMSO. The oxidation conditions reported by Reetz et al [Anaew Chem., 99, p. 1186, (1987)], Angew Chem. Int. Ed. Engl., 26, p. 1141, 1987) employed oxalyl chloride and DMSO at -78°C.

The preferred oxidation method described in this invention is sulfur trioxide pyridine complex, triethylamine and DMSO at room temperature. This system provides excellent yields of the desired chiral protected amino aldehyde usable without the need for purification i.e., the need to purify kilograms of intermediates by chromatography is eliminated and large scale operations are made less hazardous. Reaction at room temperature also eliminated the need for the use of low temperature reactor which makes the process more suitable for commercial production.

The reaction may be carried out under an inert atmosphere such as nitrogen or argon, or normal or dry air, under atmospheric pressure or in a sealed reaction vessel under positive pressure. Preferred is a nitrogen atmosphere. Alternative amine bases include, for example, tri-butyl amine, tri-isopropyl amine, N-methylpiperidine, N-methyl morpholine, azabicyclononane, diisopropylethylamine, 2,2,6,6-tetramethylpiperidine, N,N-dimethylaminopyridine, or mixtures of these bases. Triethylamine is a preferred base. Alternatives to pure DMSO as solvent include mixtures of DMSO with non-protic or halogenated solvents such as tetrahydrofuran, ethyl acetate, toluene, xylene, dichloromethane, ethylene dichloride and the like. Dipolar aprotic co-solvents include acetonitrile, dimethylformamide, dimethylacetamide, acetamide, tetramethyl urea and its cyclic analog, N-methylpyrrolidone, sulfolane and the like. Rather than N,N-dibenzylphenylalaninol as the aldehyde precursor, the phenylalaninol derivatives discussed above can be used to provide the corresponding N-monosubstituted [either P¹ or P² = H] or N,N-disubstituted aldehyde.

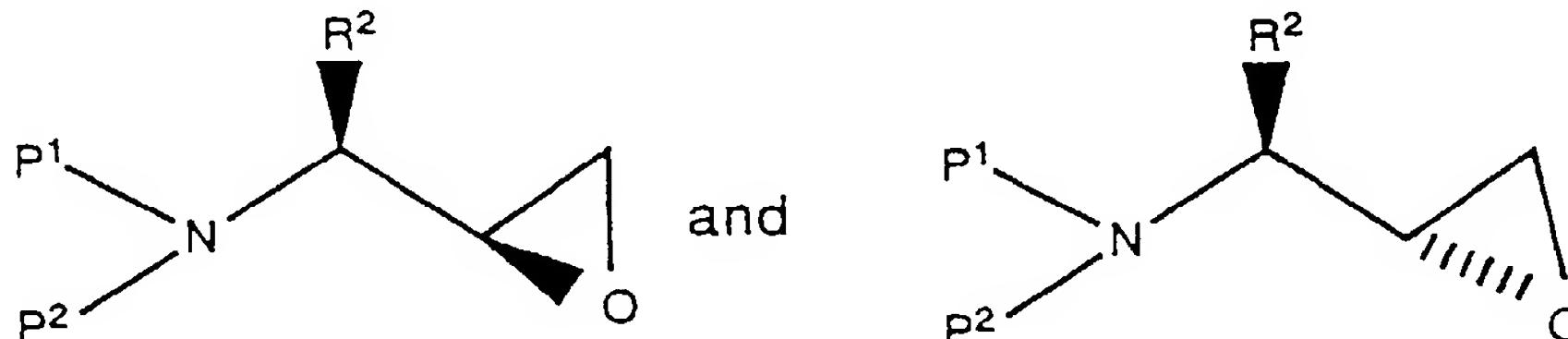
In addition, hydride reduction of an amide or ester derivative of the corresponding alkyl, benzyl or cycloalkenyl nitrogen protected phenylalanine, substituted phenylalanine or cycloalkyl analog of phenylalanine derivative can be carried out to provide the aldehydes. Hydride transfer is an additional method of aldehyde synthesis under conditions where aldehyde condensations are avoided, cf, Oppenauer Oxidation.

The aldehydes of this process can also be prepared by methods of reducing protected phenylalanine and phenylalanine analogs or their amide or ester derivatives by, e.g., sodium amalgam with HCl in ethanol or lithium or sodium or potassium or calcium in ammonia. The reaction temperature may be from about -20°C to about 45°C, and preferably from about 5°C to about 25°C. Two additional methods of obtaining the nitrogen protected aldehyde include oxidation of the corresponding alcohol with bleach in the presence of a catalytic amount of 2,2,6,6-tetramethyl-1-pyridyloxy free radical. In a second method, oxidation of the alcohol to the aldehyde is accomplished by a catalytic amount of tetrap-

ropylammonium perruthenate in the presence of N-methylmorpholine-N-oxide.

Alternatively, an acid chloride derivative of a protected phenylalanine or phenylalanine derivative as disclosed above can be reduced with hydrogen and a catalyst such as Pd on barium carbonate or barium sulphate, with or without an additional catalyst moderating agent such as sulfur or a thiol (Rosenmund Reduction).

The aldehyde resulting from the Swern oxidation is then reacted with a halomethylolithium reagent, which reagent is generated *in situ* by reacting an alkylolithium or aryllithium compound with a dihalomethane represented by the formula $X^1CH_2X^2$ wherein X^1 and X^2 independently represent I, Br or Cl. For example, a solution of the aldehyde and chloroiodomethane in THF is cooled to -78° C and a solution of n-butyllithium in hexane is added. The resulting product is a mixture of diastereomers of the corresponding amino-protected epoxides of the formulas:



The diastereomers can be separated e.g., by chromatography, or, alternatively, once reacted in subsequent steps the diastereomeric products can be separated. For compounds having the (S) stereochemistry, a D-amino acid can be utilized in place of the L-amino acid.

The addition of chloromethylolithium or bromomethylolithium to a chiral amino aldehyde is highly diastereoselective. Preferably, the chloromethylolithium or bromomethylolithium is generated *in-situ* from the reaction of the dihalomethane and n-butyllithium. Acceptable methyleneating halomethanes include chloroiodomethane, bromochloromethane, dibromomethane, diiodomethane, or bromofluoromethane. The sulfonate ester of the addition product of, for example, hydrogen bromide to formaldehyde is also a methyleneating agent. Tetrahydrofuran is the preferred solvent, however alternative solvents such as toluene, dimethoxyethane, ethylene dichloride, methylene chloride can be used as pure solvents or as a mixture. Dipolar aprotic solvents such as acetonitrile, DMF, N-methylpyrrolidone are useful as solvents or as part of a solvent mixture. The reaction can be carried out under an inert atmosphere such as nitrogen or argon. For n-butyl lithium can be substituted other organometallic reagents such as methylolithium, tert-butyl lithium, sec-butyl lithium, phenyllithium, or phenyl. The reaction can be carried out at temperatures of between about -80°C to 0°C but preferably between about -80°C to -20°C. The most preferred reaction temperatures are between -40°C to -15°C. Reagents can be added singly but multiple additions are preferred in certain conditions. The preferred pressure of the reaction is atmospheric however a positive pressure is valuable under certain conditions such as a high humidity environment.

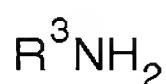
Alternative methods of conversion to the epoxides of this invention include substitution of other charged methylation precursor species followed by their treatment with base to form the analogous anion. Examples of these species include trimethylsulfoxonium tosylate or triflate, tetramethylammonium halide, methyldiphenylsulfoxonium halide wherein halide is chloride, bromide or iodide.

The conversion of the aldehydes of this invention into their epoxide derivative can also be carried out in multiple steps. For example, the addition of the anion of thioanisole prepared from, for example, a butyl or aryl lithium reagent, to the protected aminoaldehyde, oxidation of the resulting protected aminosulfide alcohol with well known oxidizing agents such as hydrogen peroxide, tert-butyl hypochlorite, bleach or sodium periodate to give a sulfoxide. Alkylation of the sulfoxide with, for example, methyl iodide or bromide, methyl tosylate, methyl mesylate, methyl triflate, ethyl bromide, isopropyl bromide, or benzyl chloride in the presence of an organic or inorganic base. Alternatively, the protected aminosulfide alcohol can be alkylated with, for example, the alkylating agents above, to provide a sulfonium salts that are subsequently converted into the subject epoxides with tert-amine or mineral bases.

The desired epoxides formed, using most preferred conditions, diastereoselectively in ratio amounts of at least about an 85:15 ratio (S:R). The product can be purified by chromatography to give the diastereomerically and enantiomerically pure product but it is more conveniently used directly without purification to prepare retroviral protease inhibitors. The foregoing process is applicable to mixtures of optical isomers as well as resolved compounds. If a particular optical isomer is desired, it can be selected by the choice of starting material, e.g., L-phenylalanine, D-phenylalanine, L-phenylalaninol, D-phenylalaninol, D-hexahydrophenylalaninol and the like, or resolution can occur at intermediate or final steps. Chiral auxiliaries such as one or two equivalents of camphor sulfonic acid, citric acid, camphoric acid, or 2-methoxyphenylacetic acid can be used to form salts, esters or amides of the compounds of this invention. These compounds or derivatives can be crystallized or separated chromatographically using either a chiral or achiral column as is well known to those skilled in the art.

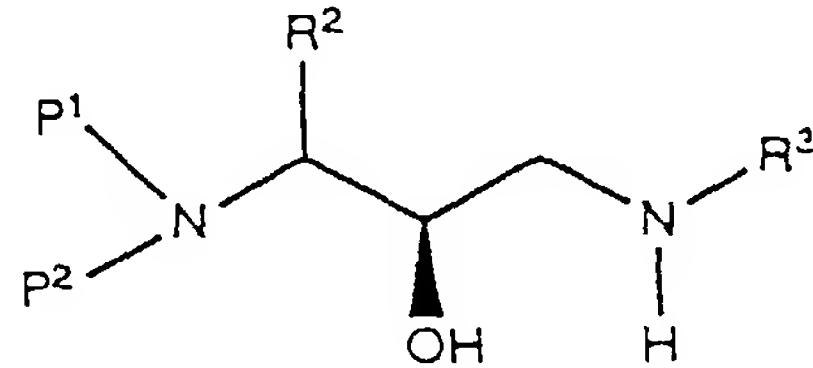
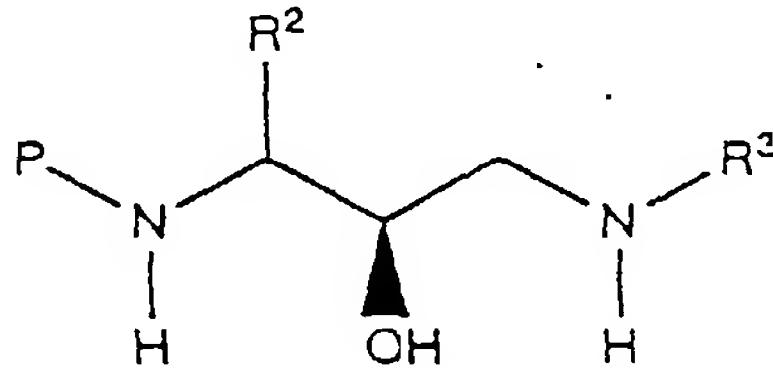
The amino epoxide is then reacted, in a suitable solvent system, with an equal amount, or preferably an excess

of, a desired amine of the formula:



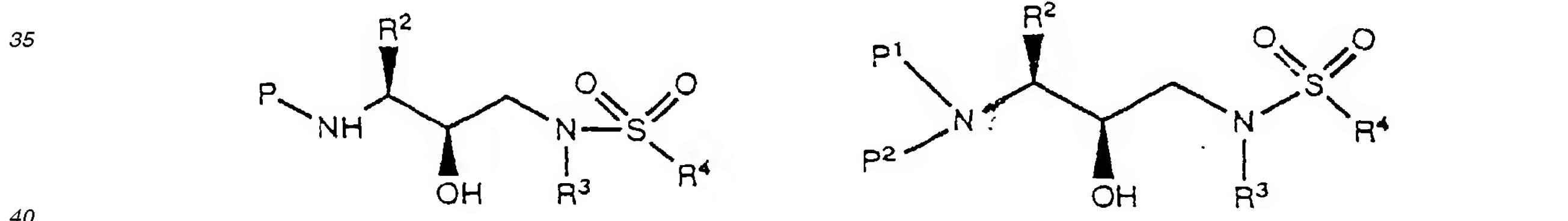
5 wherein R^3 is hydrogen or is as defined above. The reaction can be conducted over a wide range of temperatures, e.g., from about 10°C to about 100°C, but is preferably, but not necessarily, conducted at a temperature at which the solvent begins to reflux. Suitable solvent systems include protic, non-protic and dipolar aprotic organic solvents such as, for example, those wherein the solvent is an alcohol, such as methanol, ethanol, or isopropanol, ethers such as tetrahydrofuran, dioxane and the like, and toluene, N,N-dimethylformamide, dimethyl sulfoxide, and mixtures thereof. A preferred solvent is isopropanol. Exemplary amines corresponding to the formula R^3NH_2 include benzyl amine, isobutylamine, n-butyl amine, isopentyl amine, isoamylamine, cyclohexanemethyl amine, or naphthylene methyl amine. The resulting product is a 3-(N-protected amino)-3-(R^2)-1-(NHR^3)-propan-2-ol derivative (hereinafter referred to as an amino alcohol) can be represented by the formulas:

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25 wherein P, P¹, P², R² and R³ are as described above. Alternatively, a haloalcohol can be utilized in place of the amino epoxide.

The amino alcohol defined above is then reacted in a suitable solvent with a sulfonyl chloride ($\text{R}^4\text{SO}_2\text{Cl}$) or sulfonyl anhydride in the presence of an acid scavenger. Suitable solvents in which the reaction can be conducted include 30 methylene chloride, tetrahydrofuran. Suitable acid scavengers include triethylamine, pyridine. Preferred sulfonyl chlorides are methanesulfonyl chloride and benzenesulfonyl chloride. The resulting sulfonamide derivative can be represented, depending on the epoxide utilized by the formulas



wherein P, P¹, P², R², R³ and R⁴ are as defined above. These intermediates are useful for preparing inhibitor compounds of the present invention and are also active inhibitors of retroviral proteases.

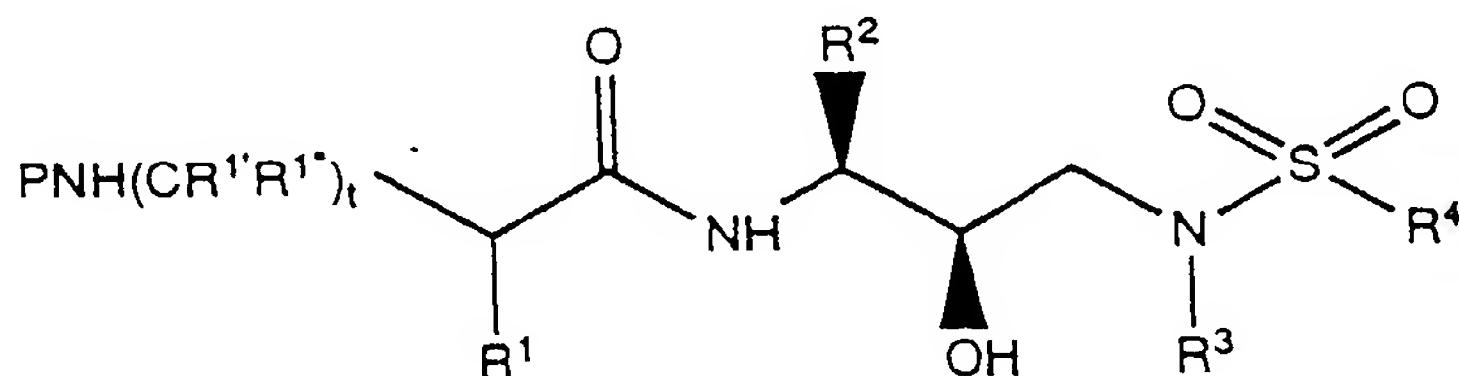
The sulfonyl halides of the formula $\text{R}^4\text{SO}_2\text{X}$ can be prepared by the reaction of a suitable Grignard or alkyl lithium reagent with sulfonyl chloride, or sulfur dioxide followed by oxidation with a halogen, preferably chlorine. Also, thiols may be oxidized to sulfonyl chlorides using chlorine in the presence of water under carefully controlled conditions. Additionally, sulfonic acids may be converted to sulfonyl halides using reagents such as PCl_5 , and also to anhydrides using suitable dehydrating reagents. The sulfonic acids may in turn be prepared using procedures well known in the art. Such sulfonic acids are also commercially available. In place of the sulfonyl halides, sulfinyl halides (R^4SOX) or sulfenyl halides (R^4SX) can be utilized to prepare compounds wherein the $-\text{SO}_2-$ moiety is replaced by an $-\text{SO}-$ or $-\text{S}-$ moiety, respectively.

Following preparation of the sulfonamide derivative, the amino protecting group P or P¹ and P² amino protecting groups are removed under conditions which will not affect the remaining portion of the molecule. These methods are well known in the art and include acid hydrolysis, hydrogenolysis and the like. A preferred method involves removal of the protecting group, e.g., removal of a carbobenzoxy group, by hydrogenolysis utilizing palladium on carbon in a suitable solvent system such as an alcohol, acetic acid, and the like or mixtures thereof. Where the protecting group is a t-butoxycarbonyl group, it can be removed utilizing an inorganic or organic acid, e.g., HCl or trifluoroacetic acid, in a suitable solvent system, e.g., dioxane or methylene chloride. The resulting product is the amine salt derivative.

Following neutralization of the salt, the amine is then reacted with an amino acid or corresponding derivative thereof represented by the formula $(PN[CR^{1'}R^{1''}]_t CH(R^1)COOH)$ wherein t, R¹, R^{1'} and R^{1''} are as defined above, to produce the antiviral compounds of the present invention having the formula:

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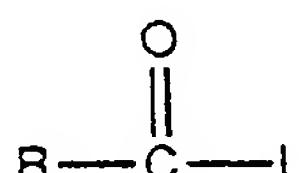


wherein t, P, R¹, R^{1'}, R^{1''}, R², R³ and R⁴ are as defined above. Preferred protecting groups in this instance are a benzyloxycarbonyl group or a t-butoxycarbonyl group. Where the amine is reacted with a derivative of an amino acid, e.g., when t=1 and R^{1'} and R^{1''} are both H, so that the amino acid is a β -amino acid, such β -amino acids can be prepared according to the procedure set forth in a copending application, U. S. Serial No. 07/345,808. Where t is 1, one of R^{1'} and R^{1''} is H and R¹ is hydrogen so that the amino acid is a homo- β -amino acid, such homo- β -amino acids can be prepared by the procedure set forth in a copending application, U.S. Serial No. 07/853,561. Where t is 0 and R¹ is alkyl, alkenyl, alkynyl, cycloalkyl, -CH₂SO₂NH₂, -CH₂CO₂CH₃, -CO₂CH₃, -CONH₂, -CH₂C(O)NHCH₃, -C(CH₃)₂(SH), -C(CH₃)₂(SCH₃), -C(CH₃)₂[S(O)CH₃], -C(CH₃)₂[S(O₂)CH₃], or an amino acid side chain, such materials are well known and many are commercially available from Sigma-Aldrich.

The N-protecting group can be subsequently removed, if desired, utilizing the procedures described above, and then reacted with a carboxylate represented by the formula:

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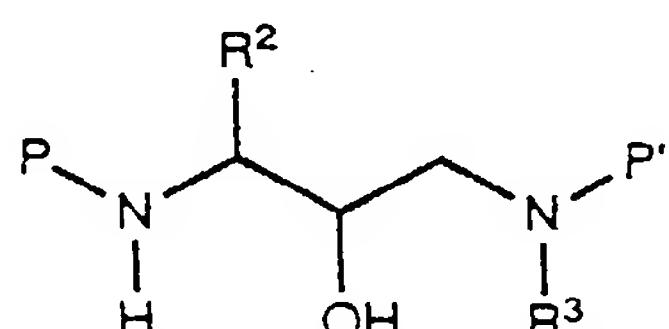


wherein R is as defined above and L is an appropriate leaving group such as a halide. Preferably, where R¹ is a side chain of a naturally occurring α -amino acid, R is a 2-quinoline carbonyl group derived from N-hydroxysuccinimide-2-quinoline carboxylate, i.e., L is hydroxy succinimide. A solution of the free amine (or amine acetate salt) and about 1.0 equivalent of the carboxylate are mixed in an appropriate solvent system and optionally treated with up to five equivalents of a base such as, for example, N-methylmorpholine, at about room temperature. Appropriate solvent systems include tetrahydrofuran, methylene chloride or N,N-dimethylformamide, and the like, including mixtures thereof.

Alternatively, the protected amino alcohol from the epoxide opening can be further protected at the newly introduced amino group with a protecting group P' which is not removed when the first protecting P is removed. One skilled in the art can choose appropriate combinations of P and P'. One suitable choice is when P is Cbz and P' is Boc. The resulting compound represented by the formula:

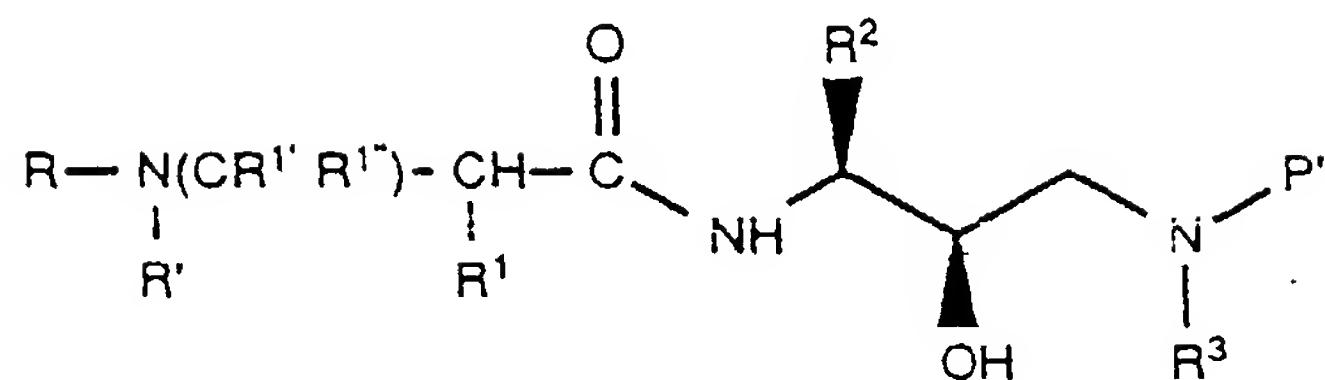
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can be carried through the remainder of the synthesis to provide a compound of the formula:

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10 and the new protecting group P' is selectively removed, and following deprotection, the resulting amine reacted to form the sulfonamide derivative as described above. This selective deprotection and conversion to the sulfonamide can be accomplished at either the end of the synthesis or at any appropriate intermediate step if desired.

In place of the sulfonyl halides, sulfinyl halides (RSOCl) and sulfenyl halides (RSCl) can be utilized to prepare compounds wherein the -SO_2^- moiety is replaced by $\text{-SO}-$ or $\text{-S}-$, respectively.

15 It is contemplated that for preparing compounds of the Formulas having R⁶, the compounds can be prepared following the procedure set forth above and, prior to coupling the sulfonamide derivative or analog thereof, e.g. coupling to the amino acid PNH(CH₂)_tCH(R¹)COOH, carried through a procedure referred to in the art as reductive amination. Thus, a sodium cyanoborohydride and an appropriate aldehyde or ketone can be reacted with the sulfonamide derivative compound or appropriate analog at room temperature in order to reductively aminate any of the compounds of 20 Formulas I-IV. It is also contemplated that where R³ of the amino alcohol intermediate is hydrogen, the inhibitor compounds of the present invention wherein R³ is alkyl, or other substituents wherein the α -C contains at least one hydrogen, can be prepared through reductive amination of the final product of the reaction between the amino alcohol and the amine or at any other stage of the synthesis for preparing the inhibitor compounds.

25 Contemplated equivalents of the general formulas set forth above for the antiviral compounds and derivatives as well as the intermediates are compounds otherwise corresponding thereto and having the same general properties, such as tautomers thereof as well as compounds, wherein one or more of the various R groups are simple variations of the substituents as defined therein, e.g., wherein R is a higher alkyl group than that indicated. In addition, where a substituent is designated as, or can be, a hydrogen, the exact chemical nature of a substituent which is other than hydrogen at that position, e.g., a hydrocarbyl radical or a halogen, hydroxy, or amino functional group, is not critical so long as it does not adversely affect the overall activity and/or synthesis procedure.

30 The chemical reactions described above are generally disclosed in terms of their broadest application to the preparation of the compounds of this invention. Occasionally, the reactions may not be applicable as described to each compound included within the disclosed scope. The compounds for which this occurs will be readily recognized by those skilled in the art. In all such cases, either the reactions can be successfully performed by conventional modifications known to those skilled in the art, e.g., by appropriate protection of interfering groups, by changing to alternative conventional reagents, by routine modification of reaction conditions, or other reactions disclosed herein or otherwise conventional, will be applicable to the preparation of the corresponding compounds of this invention. In all preparative methods, all starting materials are known or readily preparable from known starting materials.

35 Without further elaboration, it is believed that one skilled in the art can, using the preceding description, utilize the present invention to its fullest extent. The following preferred specific embodiments are, therefore, to be construed as merely illustrative.

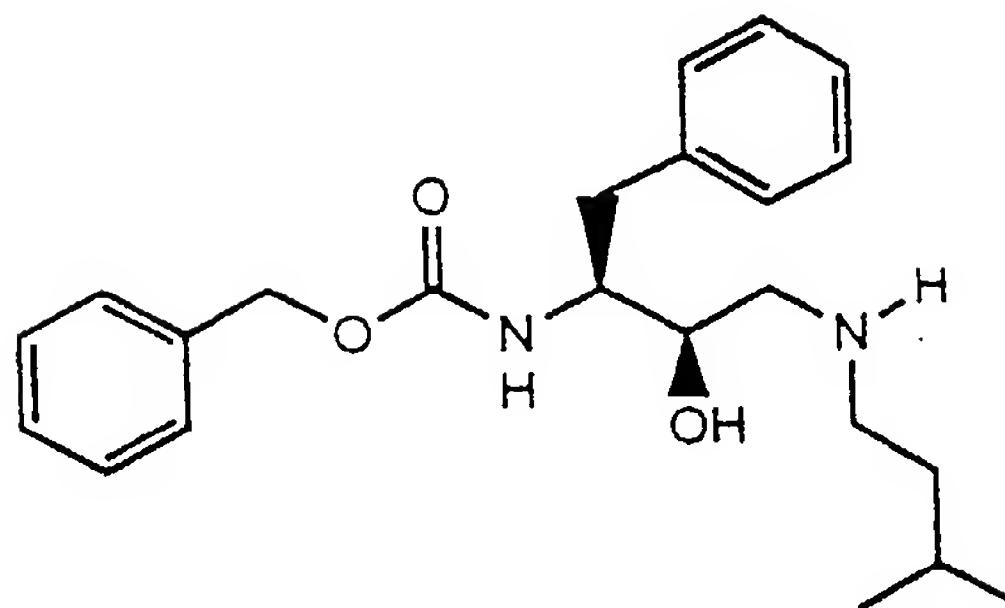
40 All reagents were used as received without purification. All proton and carbon NMR spectra were obtained on either a Varian VXR-300 or VXR-400 nuclear magnetic resonance spectrometer.

45 The following Examples 1 through 9 illustrate preparation of intermediates. These intermediates are useful in preparing the inhibitor compounds of the present invention as illustrated in Examples 10-16.

Example 1A

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Preparation of N[3(S)-benzyloxycarbonylamo-2(R)-hydroxy-4-phenylbutyl]-N-isoamylaminePart A:

To a solution of 75.0g (0.226 mol) of N-benzyloxycarbonyl-L-phenylalanine chloromethyl ketone in a mixture of 807 mL of methanol and 807 mL of tetrahydrofuran at -2°C, was added 13.17g (0.348 mol, 1.54 equiv.) of solid sodium borohydride over one hundred minutes. The solvents were removed under reduced pressure at 40°C and the residue dissolved in ethyl acetate (approx. 1L). The solution was washed sequentially with 1M potassium hydrogen sulfate, saturated sodium bicarbonate and then saturated sodium chloride solutions. After drying over anhydrous magnesium sulfate and filtering, the solution was removed under reduced pressure. To the resulting oil was added hexane (approx. 1L) and the mixture warmed to 60°C with swirling. After cooling to room temperature, the solids were collected and washed with 2L of hexane. The resulting solid was recrystallized from hot ethyl acetate and hexane to afford 32.3g (43% yield) of N-benzyloxycarbonyl-3 (S)-amino-1-chloro-4-phenyl-2(S)-butanol, mp 150-151°C and M+Li⁺ = 340.

Part B:

To a solution of 6.52g (0.116 mol, 1.2 equiv.) of potassium hydroxide in 968 mL of absolute ethanol at room temperature, was added 32.3g (0.097 mol) of N-CBZ-3(S)-amino-1-chloro-4-phenyl-2(S)-butanol. After stirring for fifteen minutes, the solvent was removed under reduced pressure and the solids dissolved in methylene chloride. After washing with water, drying over magnesium sulfate, filtering and stripping, one obtains 27.9g of a white solid. Recrystallization from hot ethyl acetate and hexane afforded 22.3g (77% yield) of N-benzyloxycarbonyl-3(S)-amino-1,2(S)-epoxy-4-phenylbutane, mp 102-103°C and MH⁺ 298.

Part C:

A solution of N-benzyloxycarbonyl 3(S)-amino-1,2-(S)-epoxy-4-phenylbutane (1.00g, 3.36 mmol) and isoamylamine (4.90g, 67.2 mmol, 20 equiv.) in 10 mL of isopropyl alcohol was heated to reflux for 1.5 hours. The solution was cooled to room temperature, concentrated *in vacuo* and then poured into 100 mL of stirring hexane whereupon the product crystallized from solution. The product was isolated by filtration and air dried to give 1.18g, 95% of N-[3 (S)-phenylmethylcarbamoyl]amino-2(R)-hydroxy-4-phenylbutyl]N-[(3-methylbutyl)]amine mp 108.0-109.5°C, MH⁺ m/z = 371.

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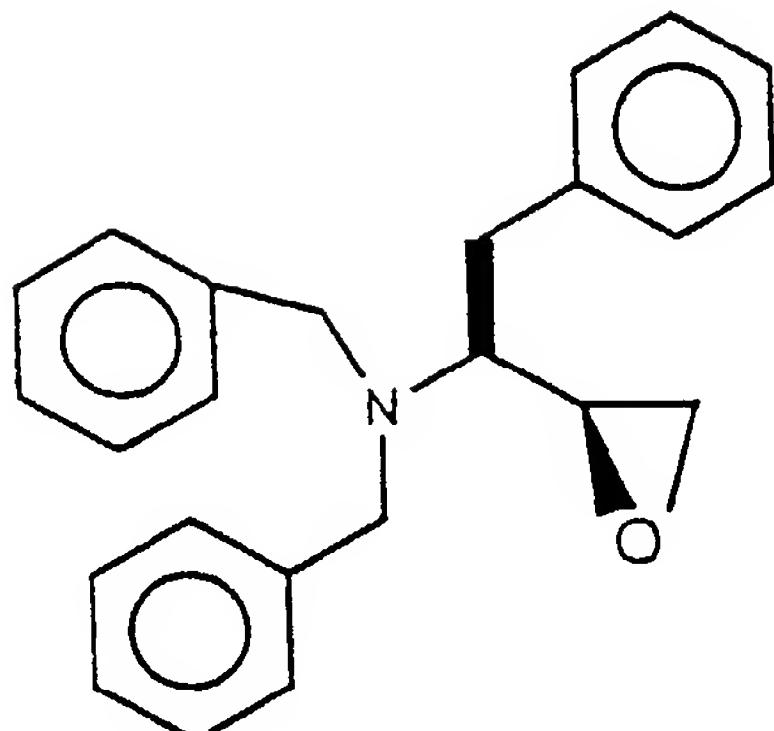
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Example 1B

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Preparation of N,N-dibenzyl-3(S)-amino-1,2-(S)-epoxy-4-phenylbutane20 Step A:

A solution of L-phenylalanine (50.0 g, 0.302 mol), sodium hydroxide (24.2 g, 0.605 mol) and potassium carbonate (83.6 g, 0.605 mol) in water (500 ml) was heated to 97°C. Benzyl bromide (108.5 ml, 0.912 mol) was then slowly added (addition time -25 min). The mixture was then stirred at 97°C for 30 minutes. The solution was cooled to room temperature and extracted with toluene (2 x 250 ml). The combined organic layers were then washed with water, brine, dried over magnesium sulfate, filtered and concentrated to give an oil product. The crude product was then used in the next step without purification.

30 Step B:

The crude benzylated product of the above step was dissolved in toluene (750 ml) and cooled to -55°C. A 1.5 M solution of DIBAL-H in toluene (443.9 ml, 0.666 mol) was then added at a rate to maintain the temperature between -55° to -50°C (addition time - 1 hour). The mixture was stirred for 20 minutes at -55°C. The reaction was quenched at -55°C by the slow addition of methanol (37 ml). The cold solution was then poured into cold (5°C) 1.5 N HCl solution (1.8 L). The precipitated solid (approx. 138 g) was filtered off and washed with toluene. The solid material was suspended in a mixture of toluene (400 ml) and water (100 ml). The mixture was cooled to 5°C, treated with 2.5 N NaOH (186 ml) and then stirred at room temperature until the solid was dissolved. The toluene layer was separated from the aqueous phase and washed with water and brine, dried over magnesium sulfate, filtered and concentrated to a volume of 75 ml (89 g). Ethyl acetate (25 ml) and hexane (25 ml) were then added to the residue upon which the alcohol product began to crystallize. After 30 min., an additional 50 ml hexane was added to promote further crystallization. The solid was filtered off and washed with 50 ml hexane to give approximately 35 g of material. A second crop of material could be isolated by refiltering the mother liquor. The solids were combined and recrystallized from ethyl acetate (20 ml) and hexane (30 ml) to give, in 2 crops, approximately 40 g (40% from L-phenylalanine) of analytically pure alcohol product. The mother liquors were combined and concentrated (34 g). The residue was treated with ethyl acetate and hexane which provided an additional 7 g (~7% yield) of slightly impure solid product. Further optimization in the recovery from the mother liquor is probable.

Alternatively, the alcohol was prepared from L-phenylalaninol. L-phenylalaninol (176.6 g, 1.168 mol) was added to a stirred solution of potassium carbonate (484.6 g, 3.506 mol) in 710 mL of water. The mixture was heated to 65°C under a nitrogen atmosphere. A solution of benzyl bromide (400 g, 2.339 mol) in 3A ethanol (305 mL) was added at a rate that maintained the temperature between 60-68°C. The biphasic solution was stirred at 65°C for 55 min and then allowed to cool to 10°C with vigorous stirring. The oily product solidified into small granules. The product was diluted with 2.0 L of cap water and stirred for 5 minutes to dissolve the inorganic by products. The product was isolated by filtration under reduced pressure and washed with water until the pH is 7. The crude product obtained was air dried overnite to give a semi-dry solid (407 g) which was recrystallized from 1.1 L of ethyl acetate/heptane (1:10 by volume). The product was isolated by filtration (at -8°C), washed with 1.6 L of cold (-10°C) ethyl acetate/heptane (1:10 by volume) and air-dried to give 339 g (88% yield) of βS-2-[Bis(phenylmethyl)amino]benzene-propanol, mp 71.5-73.0°C. More product can be obtained from the mother liquor if necessary. The other analytical characterization was identical to compound prepared as described above.

Step C:

A solution of oxalyl chloride (8.4 ml, 0.096 mol) in dichloromethane (240 ml) was cooled to -74°C. A solution of DMSO (12.0 ml, 0.155 mol) in dichloromethane (50 ml) was then slowly added at a rate to maintain the temperature at -74°C (addition time -1.25 hr). The mixture was stirred for 5 min. followed by addition of a solution of the alcohol (0.074 mol) in 100 ml of dichloromethane (addition time -20 min., temp. -75°C to -68°C). The solution was stirred at -78°C for 35 minutes. Triethylamine (41.2 ml, 0.295 mol) was then added over 10 min. (temp. -78° to -68°C) upon which the ammonium salt precipitated. The cold mixture was stirred for 30 min. and then water (225 ml) was added. The dichloromethane layer was separated from the aqueous phase and washed with water, brine, dried over magnesium sulfate, filtered and concentrated. The residue was diluted with ethyl acetate and hexane and then filtered to further remove the ammonium salt. The filtrate was concentrated to give the desired aldehyde product. The aldehyde was carried on to the next step without purification.

Temperatures higher than -70°C have been reported in the literature for the Swern oxidation. Other Swern modifications and alternatives to the Swern oxidations are also possible.

Alternatively, the aldehyde was prepared as follows. (200 g, 0.604 mol) was dissolved in triethylamine (300 mL, 2.15 mol). The mixture was cooled to 12°C and a solution of sulfur trioxide/pyridine complex (380 g, 2.39 mol) in DMSO (1.6 L) was added at a rate to maintain the temperature between 8-17°C (addition time - 1.0 h). The solution was stirred at ambient temperature under a nitrogen atmosphere for 1.5 hour at which time the reaction was complete by TLC analysis (33% ethyl acetate/hexane, silica gel). The reaction mixture was cooled with ice water and quenched with 1.6 L of cold water (10-15°C) over 45 minutes. The resultant solution was extracted with ethyl acetate (2.0 L), washed with 5% citric acid (2.0 L), and brine (2.2 L), dried over MgSO₄ (280 g) and filtered. The solvent was removed on a rotary evaporator at 35-40°C and then dried under vacuum to give 198.8 g of αS-[Bis-(phenylmethyl)amino]-benzenepropanaldehyde as a pale yellow oil (99.9%). The crude product obtained was pure enough to be used directly in the next step without purification. The analytical data of the compound were consistent with the published literature. [α]_D²⁵ = -92.9 ° (c 1.87, CH₂Cl₂); ¹H NMR (400 MHz, CDCl₃) δ, 2.94 and 3.15 (ABX-System, 2H, J_{AB}= 13.9 Hz, J_{AX}= 7.3 Hz and J_{BX}= 6.2 Hz), 3.56 (t, 1H, 7.1 Hz), 3.69 and 3.82 (AB-System, 4H, J_{AB}= 13.7 Hz), 7.25 (m, 15 H) and 9.72 (s, 1H); HRMS calcd for (M+1) C₂₃H₂₄NO 330.450, found: 330.1836. Anal. Calcd. for C₂₃H₂₃ON: C, 83.86; H, 7.04; N, 4.25. Found: C, 83.64; H, 7.42; N, 4.19. HPLC on chiral stationary phase:IS,S) Pirkle-Whelk-O 1 column (250 x 4.6 mm I. D.), mobile phase: hexane/isopropanol (99.5:0.5, v/v), flow-rate: 1.5 ml/min, detection with UV detector at 210nm. Retention time of the desired S-isomer: 8.75 min., retention time of the R-enantiomer 10.62 min.

Step D:

A solution of αS-[Bis(phenylmethyl)amino] benzene-propanaldehyde (191.7 g, 0.58 mol) and chloroiodomethane (56.4 mL, 0.77 mol) in tetrahydrofuran (1.8 L) was cooled to -30 to -35°C (colder temperature such as -70°C also worked well but warmer temperatures are more readily achieved in large scale operations) in a stainless steel reactor under a nitrogen atmosphere. A solution of n-butyllithium in hexane (1.6 M, 365 mL, 0.58 mol) was then added at a rate that maintained the temperature below -25°C. After addition the mixture was stirred at -30 to -35°C for 10 minutes. More additions of reagents were carried out in the following manner: (1) additional chloroiodomethane (17 mL) was added, followed by n-butyllithium (110 mL) at < -25°C. After addition the mixture was stirred at -30 to -35°C for 10 minutes. This was repeated once. (2) Additional chloroiodomethane (8.5 mL, 0.11 mol) was added, followed by n-butyllithium (55 mL, 0.088 mol) at <-25°C. After addition, the mixture was stirred at -30 to -35°C for 10 minutes. This was repeated 5 times. (3) Additional chloroiodomethane (8.5 mL, 0.11 mol) was added, followed by n-butyllithium (37 mL, 0.059 mol) at <-25°C. After addition, the mixture was stirred at -30 to -35°C for 10 minutes. This was repeated once. The external cooling was stopped and the mixture warmed to ambient temp. over 4 to 16 hours when TLC (silica gel, 20% ethyl acetate/hexane) indicated that the reaction was completed. The reaction mixture was cooled to 10°C and quenched with 1452 g of 16% ammonium chloride solution (prepared by dissolving 232 g of ammonium chloride in 1220 mL of water), keeping the temperature below 23°C. The mixture was stirred for 10 minutes and the organic and aqueous layers were separated. The aqueous phase was extracted with ethyl acetate (2x 500 mL). The ethyl acetate layer was combined with the tetrahydrofuran layer. The combined solution was dried over magnesium sulfate (220 g), filtered and concentrated on a rotary evaporator at 65°C. The brown oil residue was dried at 70°C in vacuo (0.8 bar) for 1 h to give 222.8 g of crude material. (The crude product weight was >100%. Due to the relative instability of the product on silica gel, the crude product is usually used directly in the next step without purification). The diastereomeric ratio of the crude mixture was determined by proton NMR: (2S)/(2R): 86:14. The minor and major epoxide diastereomers were characterized in this mixture by tlc analysis (silica gel, 10% ethyl acetate/hexane), R_f = 0.29 & 0.32, respectively. An analytical sample of each of the diastereomers was obtained by purification on silica-gel chromatography (3% ethyl acetate/hexane) and characterized as follows:
N,N,αS-Tris(phenylmethyl)-2S-oxiranemethanamine

¹H NMR (400 MHz, CDCl₃) δ 2.49 and 2.51 (AB-System, 1H, J_{AB} = 2.82), 2.76 and 2.77 (AB-System, 1H, J_{AB} = 4.03), 2.83 (m, 2H), 2.99 & 3.03 (AB-System, 1H, J_{AB} = 10.1 Hz), 3.15 (m, 1H), 3.73 & 3.84 (AB-System, 4H, J_{AB} = 14.00), 7.21 (m, 15H); ¹³C NMR (400 MHz, CDCl₃) δ 139.55, 129.45, 128.42, 128.14, 128.09, 126.84, 125.97, 60.32, 54.23, 52.13, 45.99, 33.76; HRMS calcd for C₂₄H₂₆NO (M+1) 344.477, found 344.2003.

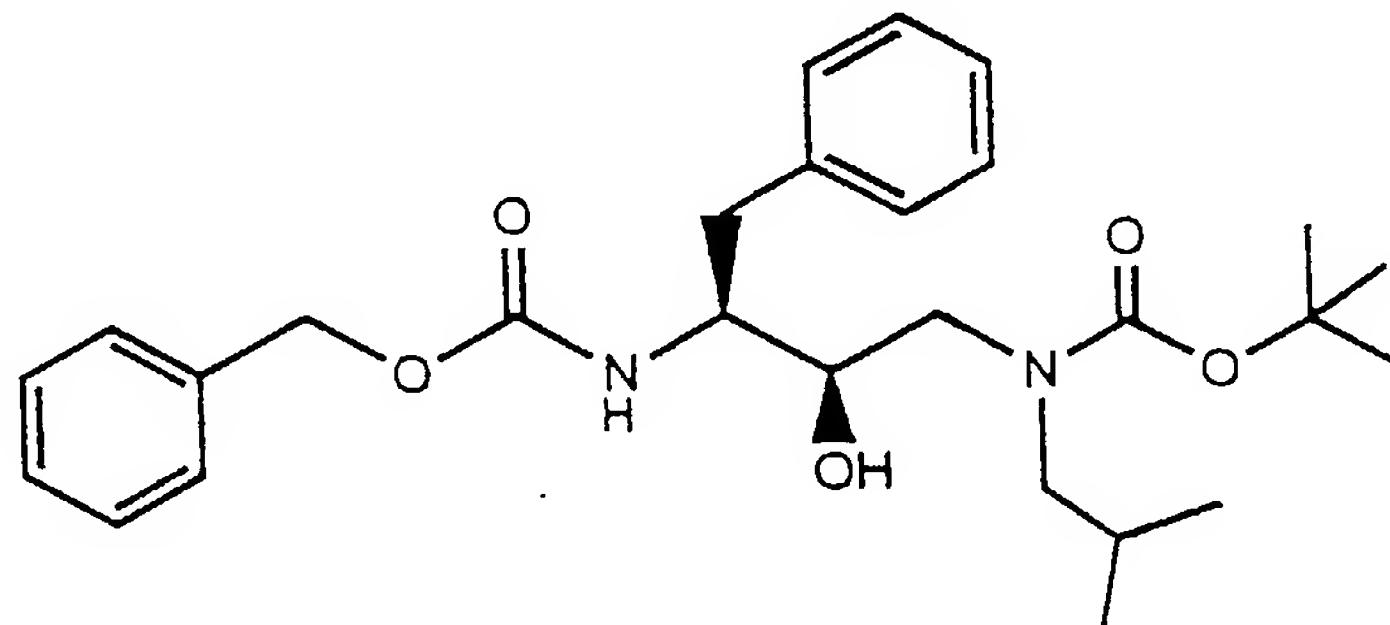
5 N,N,αS-Tris(phenylmethyl)-2R-oxiranemethanamine

1H NMR (300 MHz, CDCl₃) δ 2.20 (m, 1H), 2.59 (m, 1H), 2.75 (m, 2H), 2.97 (m, 1H), 3.14 (m, 1H), 3.85 (AB-System, 4H), 7.25 (m, 15H). HPLC on chiral stationary phase: Pirkle-Whelk-O 1 column (250 x 4.6 mm I.D.), mobile phase: hexane/isopropanol (99.5:0.5, v/v), flow-rate: 1.5 ml/min, detection with UV detector at 210nm. Retention time of (8): 9.38 min., retention time of enantiomer of (4): 13.75 min.

10 Alternatively, a solution of the crude aldehyde 0.074 mol and chloroiodomethane (7.0 ml, 0.096 mol) in tetrahydrofuran (285 ml) was cooled to -78°C, under a nitrogen atmosphere. A 1.6 M solution of n-butyllithium in hexane (25 ml, 0.040 mol) was then added at a rate to maintain the temperature at -75°C (addition time - 15 min.). After the first addition, additional chloroiodomethane (1.6 ml, 0.022 mol) was added again, followed by n-butyllithium (23 ml, 0.037 mol), keeping the temperature at -75°C. The mixture was stirred for 15 min. Each of the reagents, chloroiodomethane (0.70 ml, 0.010 mol) and n-butyllithium (5 ml, 0.008 mol) were added 4 more times over 45 min. at -75°C. The cooling bath was then removed and the solution warmed to 22°C over 1.5 hr. The mixture was poured into 300 ml of saturated aq. ammonium chloride solution. The tetrahydrofuran layer was separated. The aqueous phase was extracted with ethyl acetate (1 x 300 ml). The combined organic layers were washed with brine, dried over magnesium sulfate, filtered and concentrated to give a brown oil (27.4 g). The product could be used in the next step without purification. The desired diastereomer can be purified by recrystallization at a subsequent step. The product could also be purified by chromatography.

15 Alternatively, a solution of αS-[Bis(phenylmethyl)amino]benzene-propanaldehyde (178.84 g, 0.54 mol) and bromochloromethane (46 mL, 0.71 mol) in tetrahydrofuran (1.8 L) was cooled to -30 to -35°C (colder temperature such as -70°C also worked well but warmer temperatures are more readily achieved in large scale operations) in a stainless steel reactor under a nitrogen atmosphere. A solution of n-butyllithium in hexane (1.6 M, 340 mL, 0.54 mol) was then added at a rate that maintained the temperature below -25°C. After addition the mixture was stirred at -30 to -35°C for 10 minutes. More additions of reagents were carried out in the following manner: (1) additional bromochloromethane (14 mL) was added, followed by n-butyllithium (102 mL) at <-25°C. After addition the mixture was stirred at -30 to -35°C for 10 minutes. This was repeated once. (2) Additional bromochloromethane (7 mL, 0.11 mol) was added, followed by n-butyllithium (51 mL, 0.082 mol) at <-25°C. After addition the mixture was stirred at -30 to -35°C for 10 minutes. This was repeated 5 times. (3) Additional bromochloromethane (7 mL, 0.11 mol) was added, followed by n-butyllithium (51 mL, 0.082 mol) at <-25°C. After addition the mixture was stirred at -30 to -35°C for 10 minutes. This was repeated once. The external cooling was stopped and the mixture warmed to ambient temp. over 4 to 16 hours when TLC (silica gel, 20% ethyl acetate/hexane) indicated that the reaction was completed. The reaction mixture was cooled to 10°C and quenched with 1452 g of 16% ammonium chloride solution (prepared by dissolving 232 g of ammonium chloride in 1220 mL of water), keeping the temperature below 23°C. The mixture was stirred for 10 minutes and the organic and aqueous layers were separated. The aqueous phase was extracted with ethyl acetate (2x 500 mL). The ethyl acetate layer was combined with the tetrahydrofuran layer. The combined solution was dried over magnesium sulfate (220 g), filtered and concentrated on a rotary evaporator at 65°C. The brown oil residue was dried at 70°C in vacuo (0.8 bar) for 1 h to give 222.8 g of crude material.

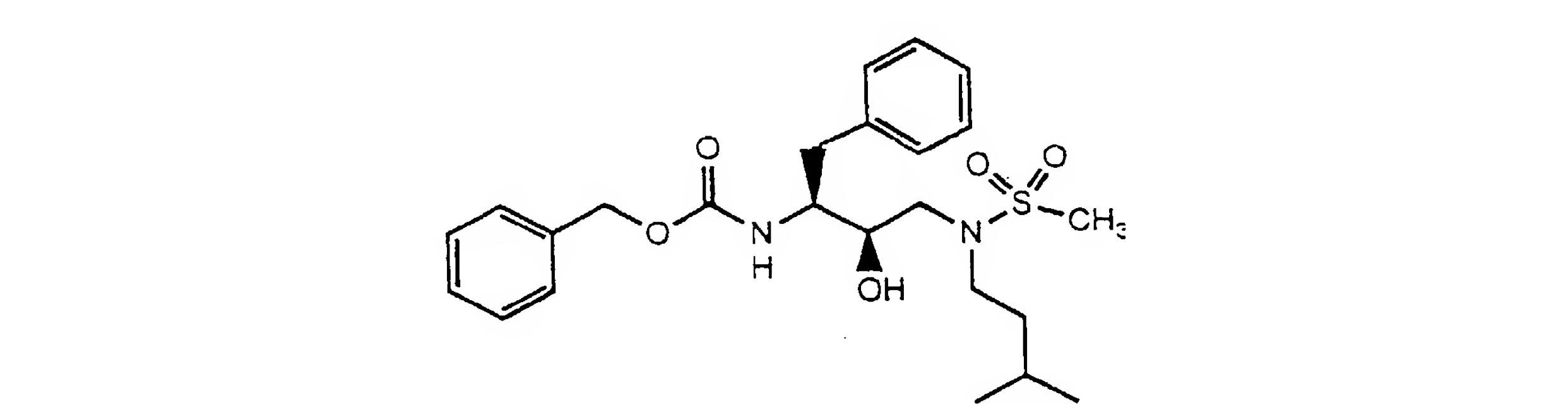
Example 2



Preparation of N-[3S-(phenylmethylcarbamoyl)amino]-2R-hydroxy-4-phenyl]-1-[(2-methylpropyl)amino-2-(1,1-dimethylethoxyl)carbonyl]butane

To a solution of 7.51g (20.3 mmol) of N-[3S-(phenylmethylcarbamoyl)amino]-2R-hydroxy-4-phenylbutyl]-N-(2-methylpropyl)amine in 67 mL of anhydrous tetrahydrofuran was added 2.25g (22.3 mmol) of triethylamine. After cooling to 0°C, 4.4g (20.3 mmol) of di-tert-butyl dicarbonate was added and stirring continued at room temperature for 21 hours. The volatiles were removed in vacuo, ethyl acetate added, then washed with 5% citric acid, saturated sodium bicarbonate, brine, dried over magnesium sulfate, filtered and concentrated to afford 9.6g of crude product. Chromatography on silica gel using 30% ethyl acetate/hexane afforded 8.2g of pure N-[3S-(phenylmethylcarbamoyl)amino]-2R-hydroxy-4-phenyl]-1-[(2-methylpropyl)amino-2-(1,1-dimethylethoxyl)carbonyl]butane, mass spectrum m/e = 477 (M+Li).

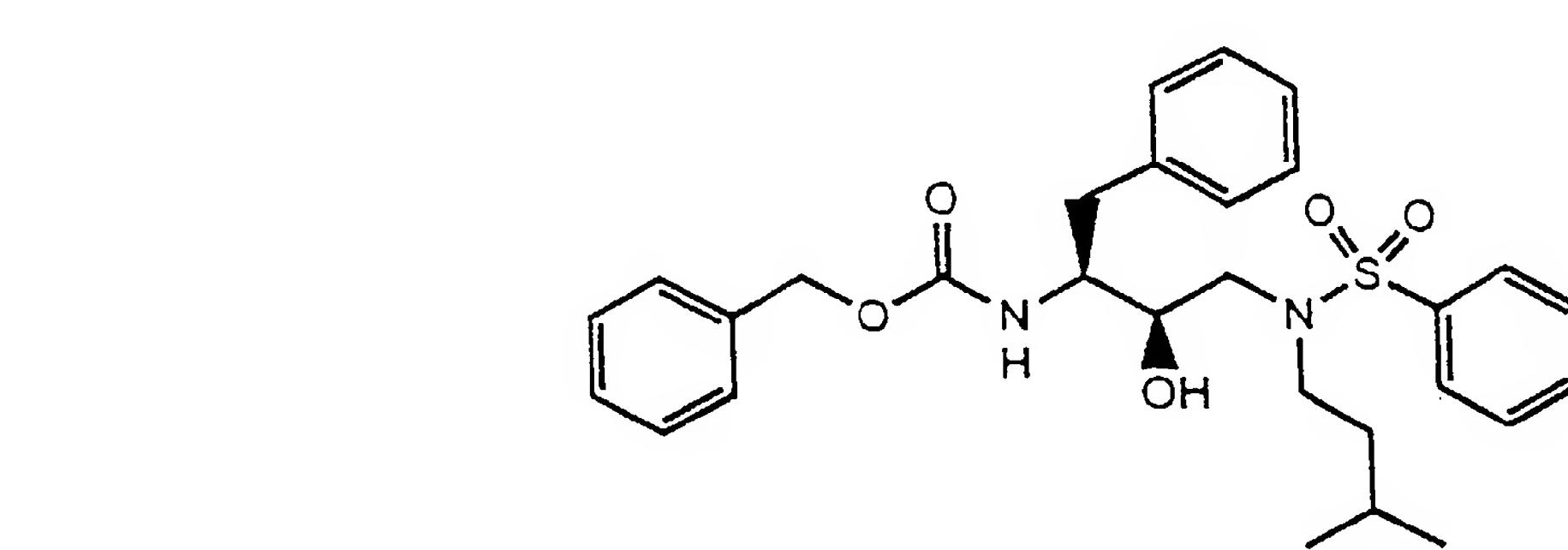
Example 3A



Preparation of phenylmethyl [2R-hydroxy-3-[(3-methylbutyl) (methylsulfonyl)amino]-1S-(phenylmethyl)propyl] carbamate

30 To a solution of N[3(S)-benzyloxycarbonylamino-2(R)-hydroxy-4-phenylbutyl] N-isoamylamine (2.0 gm, 5.2 mmol) and triethylamine (723 uL, 5.5 mmol) in dichloromethane (20 mL) was added dropwise methanesulfonyl chloride (400 uL, 5.2 mmol). The reaction mixture was stirred for 2 hours at room temperature, then the dichloromethane solution was concentrated to ca. 5 mL and applied to a silica gel column (100 gm). The column was eluted with chloroform containing 1% ethanol and 1% methanol. The phenylmethyl [2R-hydroxy-3-[(3-methylbutyl) (methylsulfonyl)amino]-1S-(phenylmethyl)propyl]carbamate was obtained as a white solid Anal. Calcd for C₂₄H₃₄N₂O₅S: C, 62.31; H, 7.41; N, 6.06. Found: C, 62.17; H, 7.55; N, 5.97.

Example 3B



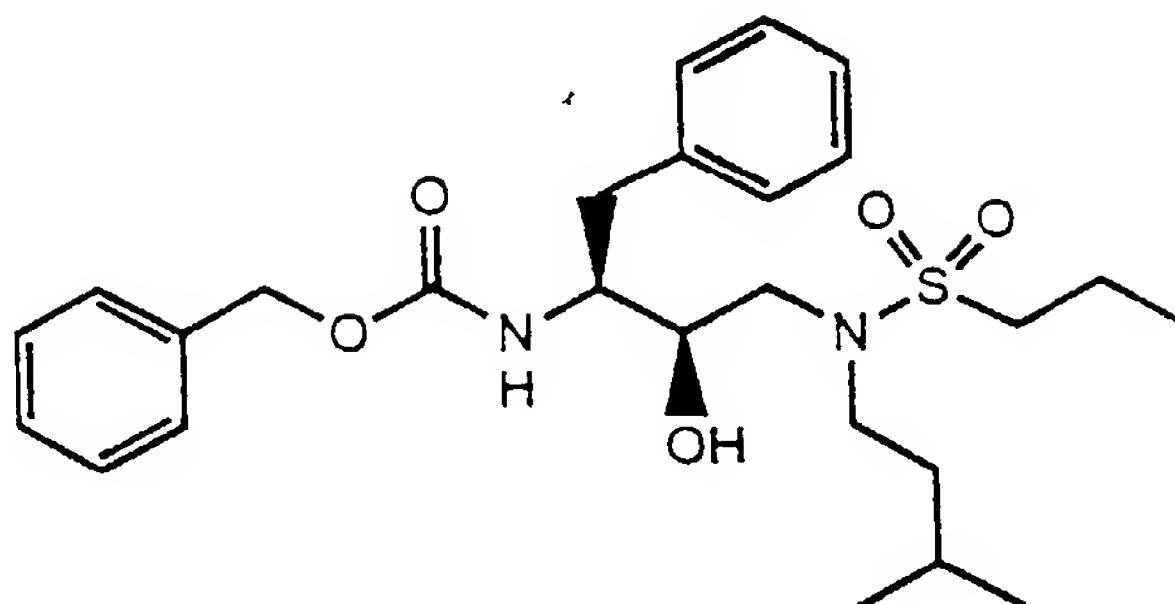
Preparation of phenylmethyl [2R-hydroxy-3-[(3-methylbutyl) (phenylsulfonyl)amino]-1S-(phenylmethyl)propyl] carbamate

55 From the reaction of N[3(S)-benzyloxycarbonylamino-2(R)-hydroxy-4-phenylbutyl] N-isoamylamine (1.47 gm, 3.8 mmol), triethylamine (528 uL, 3.8 mmol) and benzenesulfonyl chloride (483 uL, 3.8 mmol) one obtains phenylmethyl [2R-hydroxy-3-[(3-methylbutyl) (phenylsulfonyl)amino]-1S-(phenylmethyl)propyl]-carbamate. Column chromatography on silica gel eluting with chloroform containing 1% ethanol afforded the pure product. Anal. Calcd for C₂₉H₃₆N₂O₅S:

C, 66.39; H, 6.92; N, 5.34. Found: C, 66.37; H, 6.93; N, 5.26.

Example 4

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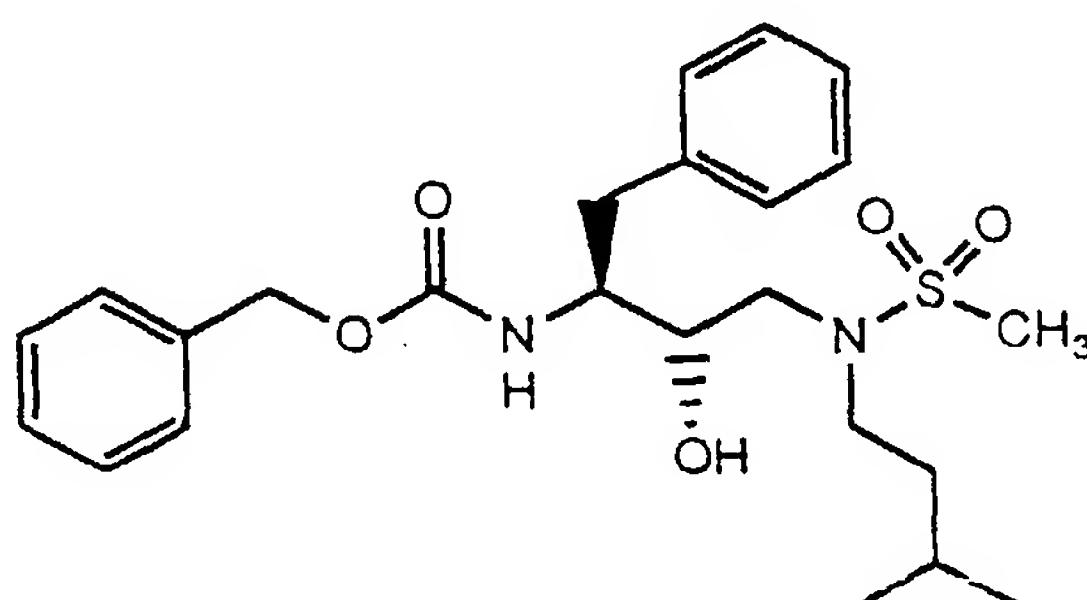
Preparation of Phenylmethyl [2R-hydroxy-3-[(3-methylbutyl) (n-propanesulfonyl)amino]-1S-(phenylmethyl)propyl] carbamate

20 To a solution of N[3(S)-benzyloxycarbonylamino-2(R)-hydroxy-4-phenylbutyl] N-isoamylamine (192 mg, 0.5 mmol) and triethylamine (139 uL, 1.0 mmol) in dichloromethane (10 mL) was added dropwise trimethylsilyl chloride (63 uL, 0.5 mmol). The reaction was allowed to stir for 1 hour at room temperature, cooled to 0° C with an ice bath and then n-propanesulfonyl chloride (56 uL, 0.5 mmol) was added dropwise. The reaction mixture was stirred for 1.5 hours at room temperature, then diluted with ethyl acetate (50 mL) and washed sequentially with 1N HCl, water, saturated sodium bicarbonate solution, and saturated sodium chloride solution (25 mL each). The organic solution was dried over magnesium sulfate, filtered and concentrated to an oil. The oil was stirred with methanol (10 mL) for 16 hours, concentrated and the residue chromatographed on silica gel (50 gm) eluting with 10% ethyl acetate in hexane (450 mL), then with 1:1 ethyl acetate / hexane. The phenylmethyl [2R-hydroxy-3-[(3-methylbutyl) (n-propanesulfonyl)amino]-1S-(phenylmethyl)propyl]carbamate was recrystallized from ethyl ether / hexane to afford a white solid Anal. Calcd. for C₂₆H₃₈N₂O₅S: C, 63.64; H, 7.81; N, 5.71. Found: C, 63.09; H, 7.74; N, 5.64.

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Example 5

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The procedure described in Example 2 was used to prepare phenylmethyl [2S-hydroxy-3-[(3-methylbutyl) (methylsulfonyl)amino]-1S-(phenylmethyl)propyl]carbamate.

To a solution of N[3(S)-benzyloxycarbonylamino-2(S)-hydroxy-4-phenylbutyl] N-isoamylamine (192 mg, 0.5 mmol) and triethylamine (139 uL, 0.55 mmol) in dichloromethane (8 mL) was added dropwise methanesulfonyl chloride (39 uL, 0.55 mmol). The reaction mixture was stirred for 16 hours at room temperature, then the dichloromethane solution was applied to a silica gel column (50 gm). The column was eluted with dichloromethane containing 2.5% methanol. The phenylmethyl [2S-hydroxy-3-[(3-methylbutyl) (methylsulfonyl)amino]-1S-(phenylmethyl)propyl]carbamate was obtained as a white solid Anal. Calcd. for C₂₄H₃₄N₂O₅S + 0.2 H₂O: C, 61.83; H, 7.44; N, 6.01. Found: C, 61.62; H, 7.40; N, 5.99.

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Example 6

Following the procedures of the previous Examples 1-5, the intermediate compounds set forth in Tables 1A and

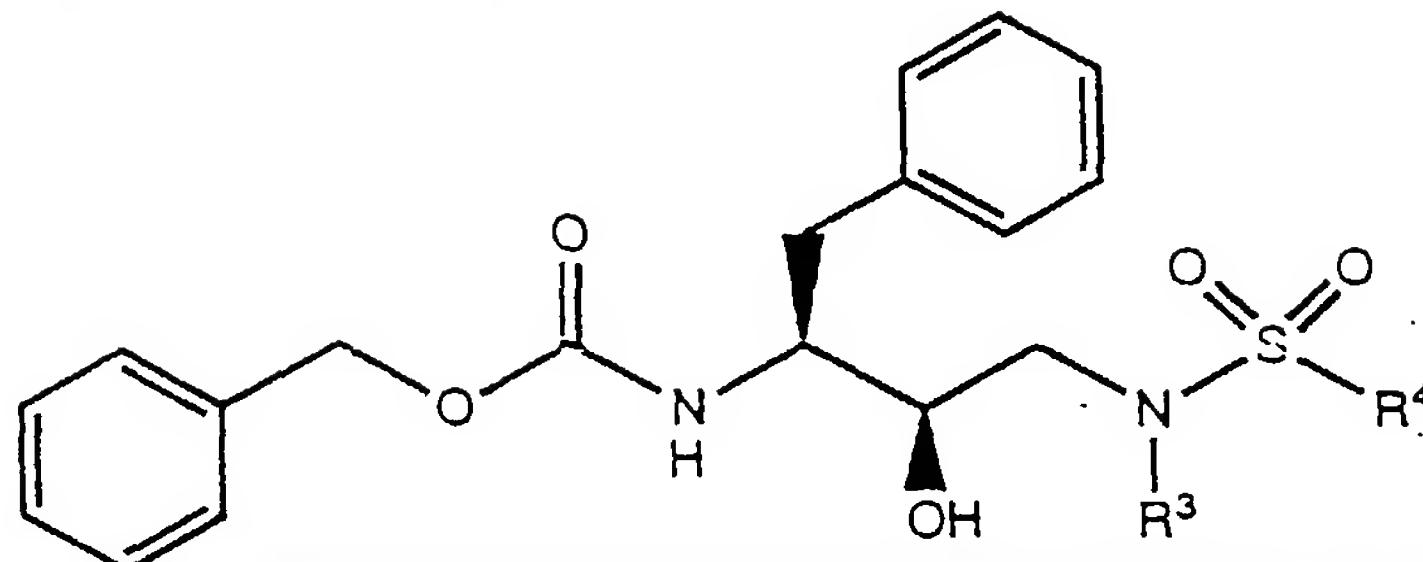
1B were prepared.

TABLE 1A

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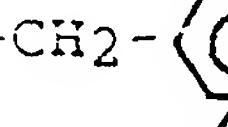
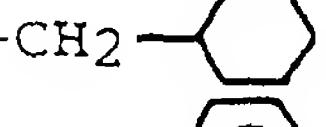
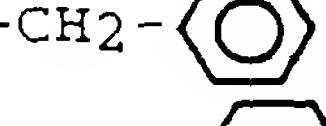
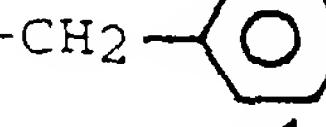
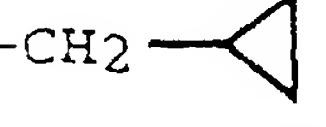
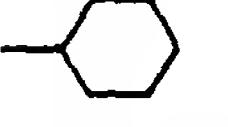
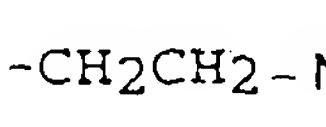
Entry	R ³	R ⁴
1	isoamyl	p-fluorophenyl
2	isoamyl	p-nitrophenyl
3	isoamyl	o-nitrophenyl
4	isoamyl	β-naphthyl
5	isoamyl	2-thienyl
6	isoamyl	benzyl
7	isobutyl	p-fluorophenyl
8	p-fluorobenzyl	phenyl
9	4-pyridylmethyl	phenyl
10	cyclohexylmethyl	phenyl
11	allyl	phenyl
12	propyl	phenyl
13	cyclopropylmethyl	phenyl
14	methyl	phenyl
15	propargyl	phenyl
16	isoamyl	p-chlorophenyl

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TABLE 1A (Cont'd)

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Entry	R ³	R ⁴
10	17 isoamyl	p-methoxyphenyl
	18 isoamyl	m-nitrophenyl
	19 isoamyl	m-trifluoromethylphenyl
15	20 isoamyl	o-methoxycarbonylphenyl
	21 isoamyl	p-acetamidophenyl
	22 isobutyl	phenyl
20	23 -CH ₂ Ph	-Ph
	24 -CH ₂ -  -F	-Ph
	25 -CH ₂ - 	-Ph
25	26 -CH ₂ -  -OCH ₃	-Ph
	27 -CH ₂ - 	-Ph
	28 -CH ₂ - 	-Ph
30	29 -CH ₂ CH=CH ₂	-Ph
	30 - 	-Ph
	31 - 	-Ph
35	32 -CH ₂ CH ₂ Ph	-Ph
	33 -CH ₂ CH ₂ CH ₂ CH ₂ OH	-Ph
	34 -CH ₂ CH ₂ N(CH ₃) ₂	-Ph
40	35 -CH ₂ CH ₂ -N 	-Ph
	36 -CH ₃	-Ph
	37 -CH ₂ CH ₂ CH ₂ SCH ₃	-Ph
45	38 -CH ₂ CH ₂ CH ₂ S(O)CH ₃	-Ph
	39 -CH ₂ CH ₂ CH(CH ₃) ₂	- 
	40 -CH ₂ CH ₂ CH(CH ₃) ₂	-CH ₂ CH ₂ CH ₃

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TABLE 1A (Cont'd)

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	Entry	R ³	R ⁴
10	41	-CH ₂ CH ₂ CH(CH ₃) ₂	-CH ₃
	42	-CH ₂ CH ₂ CH(CH ₃) ₂	-
15	43	-CH ₂ CH ₂ CH(CH ₃) ₂	-
	44	-CH ₂ CH ₂ CH(CH ₃) ₂	CO ₂ CH ₃ -
20	45	-CH ₂ CH(CH ₃) ₂	-
	46	-CH ₂ CH(CH ₃) ₂	-
25	47	-CH ₂ CH(CH ₃) ₂	-
	48	-CH ₂ CH ₂ CH ₃	-
	49	-CH ₂ CH ₂ CH ₂ CH ₃	-
30	50	-CH ₂ CH ₂ CH(CH ₃) ₂	-CF ₃
	51	-CH ₂ CH(CH ₃) ₂	-CH ₃
	52	-CH ₂ CH ₂ CH(CH ₃) ₂	-CH ₂ Cl
35	53	-CH ₂ CH(CH ₃) ₂	-CH ₂ =CH-
	54	-CH ₂ CH(CH ₃) ₂	-
	55	-CH ₂ CH(CH ₃) ₂	-CH=CH ₂
40	56	-CH ₂ (-CH)CH ₃) (CH ₂ CH ₃)	-

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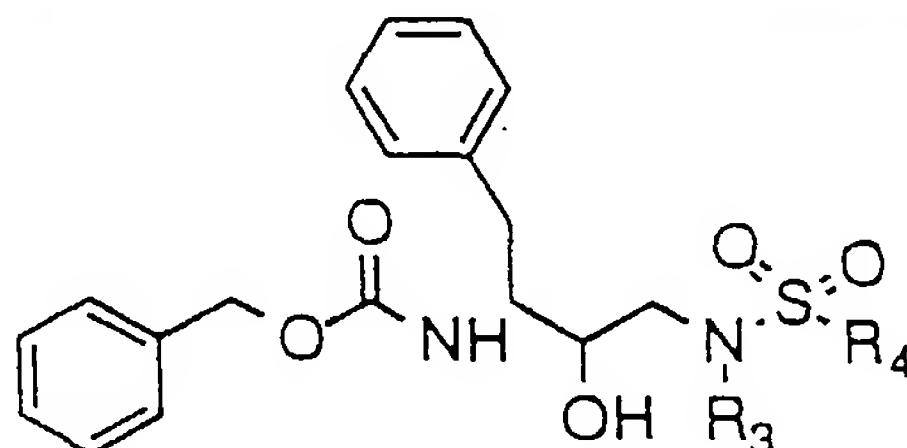
55

TABLE 1A (Cont'd)

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Entry

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MASS MEASUREMENT

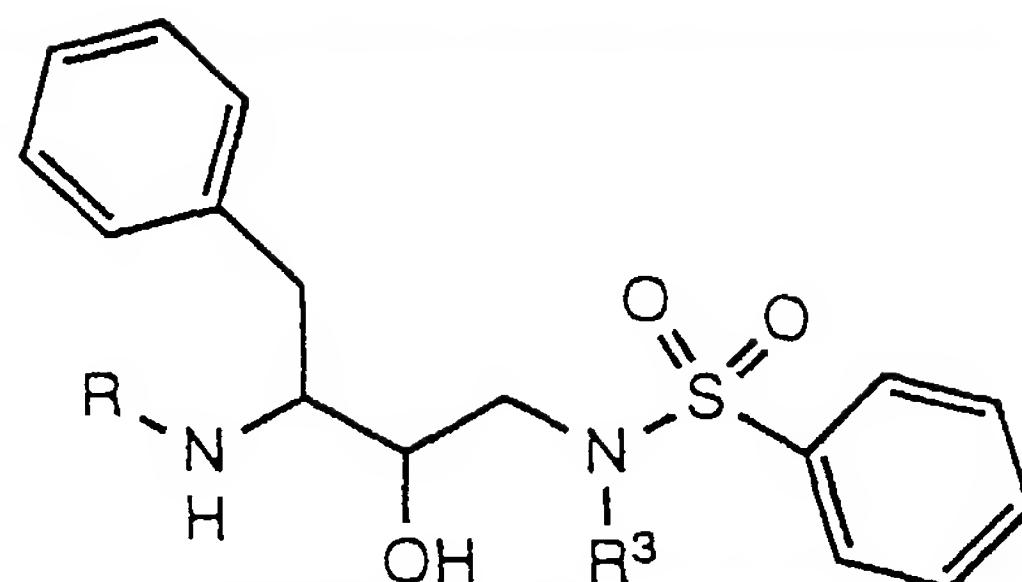
	R^3	R^4	MOL FORM	CALC	FOUND
20	1 		$\text{C}_{29}\text{H}_{36}\text{N}_2\text{O}_5\text{S}$	531 (M+Li)	531
25	2 		$\text{C}_{29}\text{H}_{36}\text{N}_2\text{O}_6\text{S}$	541 (M+H)	541
30	3 		$\text{C}_{30}\text{H}_{36}\text{N}_2\text{O}_6\text{S}$	555.2529 (M+H)	555.2582
35	4 				
40	5 				
45	6 		$\text{C}_{28}\text{H}_{33}\text{N}_2\text{O}_5\text{SF}$	529.2172 (M+H)	521.2976
50	7 				
55	8 		$\text{C}_{29}\text{H}_{36}\text{N}_2\text{O}_5\text{S}_2$	563 (M+Li)	563
	9 		$\text{C}_{29}\text{H}_{36}\text{N}_2\text{O}_6\text{S}_2$	573 (M+H)	573
	10 		$\text{C}_{29}\text{H}_{36}\text{N}_2\text{O}_7\text{S}_2$	595 (M+Li)	595

TABLE 1B

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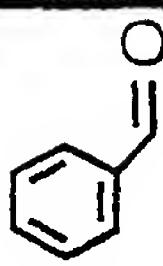
Entry

R

R³

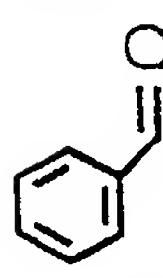
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1

-CH₂Ph

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2

-CH₂CH₂CH(CH₃)₂

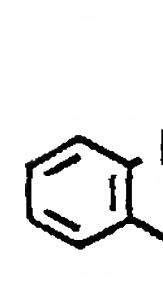
35

3

-CH₂CH(CH₃)₂

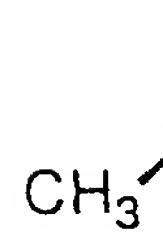
40

4

-CH₂CH(CH₃)₂

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-CH₂CH(CH₃)₂

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TABLE 1B (Cont'd)

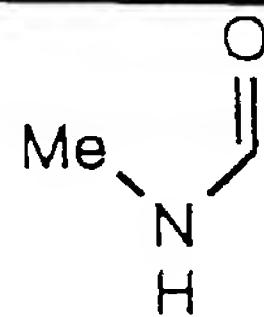
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Entry

R

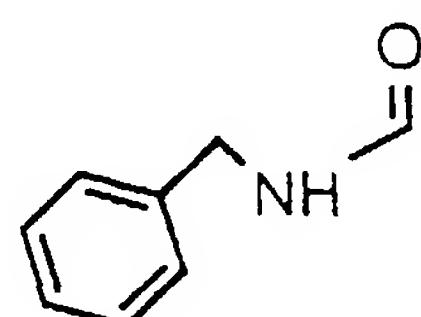
R³

10



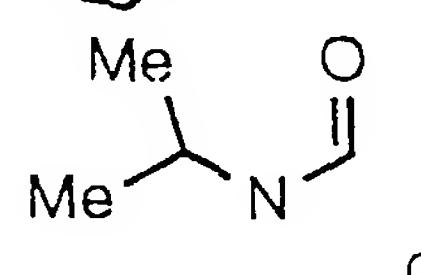
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6



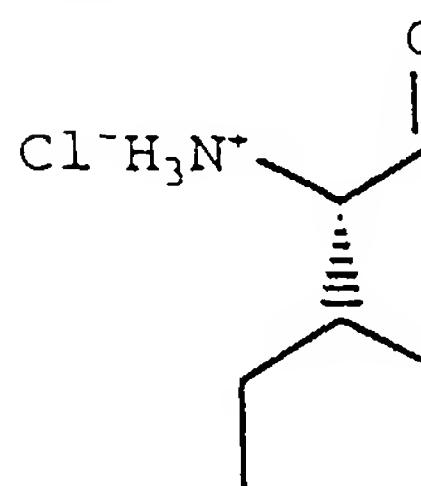
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-CH₂CH(CH₃)₂-CH₂CH(CH₃)₂-CH₂CH(CH₃)₂-CH₂CH₂(CH₃)₂

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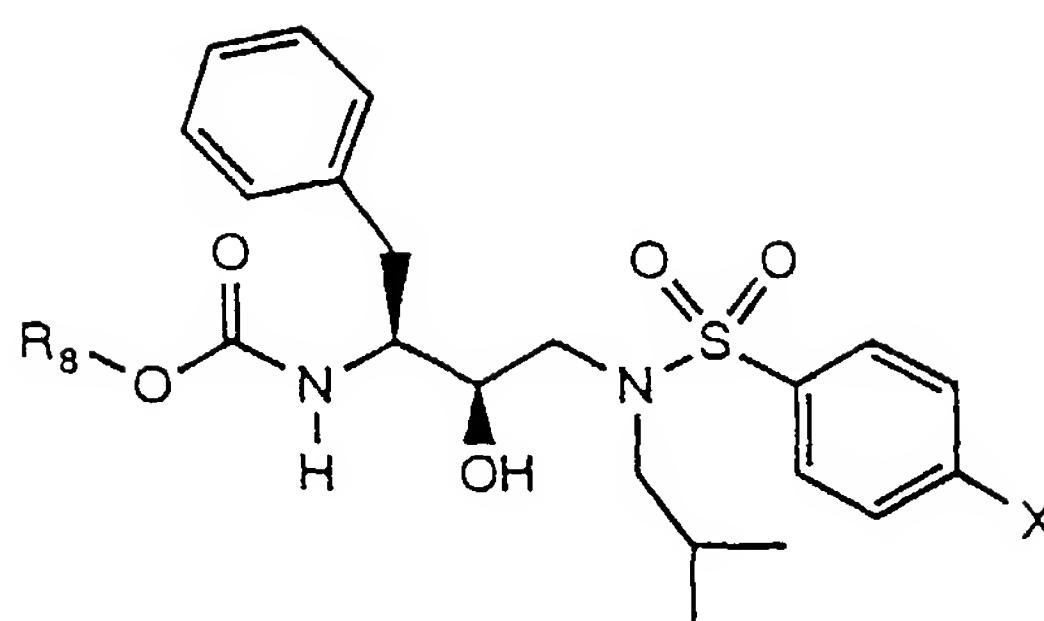
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Table 1C

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		Mass Determination		
X	R ⁸	FORMULA	Calc	Found
H		C ₂₇ H ₃₃ N ₃ O ₅ S	512.2219(M+H)	521.2267
OCH ₃		C ₂₈ H ₃₅ N ₃ O ₆ S	548.2407(M+Li)	548.2434
F		C ₂₇ H ₃₂ N ₃ O ₅ SF	530(M+H)	530
Cl		C ₂₇ H ₃₂ N ₃ O ₅ SCl	546(M+H)	546
NO ₂		C ₂₇ H ₃₂ N ₄ O ₇ S	557(M+H)	557
OH		C ₂₇ H ₃₃ N ₃ O ₆ S	528(M+H)	528

TABLE 1C (Cont'd)

5	X	R ⁸	Mass Determination		
			FORMULA	Calc	Found
10	OCH ₃		C ₂₈ H ₃₅ N ₃ O ₆ S	542.2325(M+H)	542.2362
15	OCH ₃		C ₂₈ H ₃₅ N ₃ O ₆ S	548.2407(M+Li)	548.2393
20	OCH ₃		C ₂₈ H ₃₅ N ₃ O ₆ S	543(M+H)	543
25	OCH ₃		C ₂₉ H ₃₆ O ₆ N ₂ S	547.2454(M+Li)	547.2475
30	OCH ₃	tert-Butyl	C ₂₆ H ₃₈ N ₂ O ₆ S	513.2611(M+Li)	513.2593
35	OCH ₃		C ₂₈ H ₃₅ N ₃ O ₇ S	564(M+Li)	564
40	OCH ₃		C ₂₈ H ₃₅ N ₃ O ₇ S	564(M+Li)	564

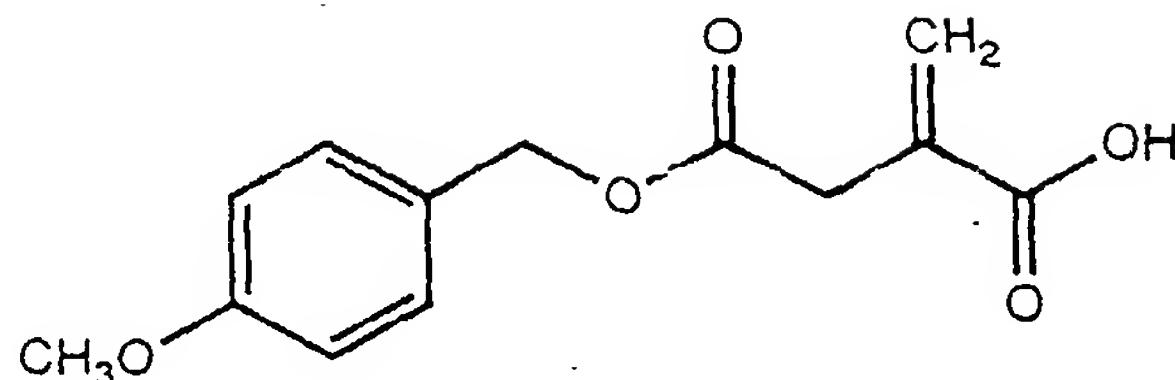
The following Examples 7-9 illustrate preparation of β -amino acid intermediates. These intermediates can be coupled to the intermediate compounds of Examples 1-6 to produce inhibitor compounds of the present invention containing β -amino acids.

Example 7

A. Preparation of 4(4-methoxybenzyl)itaconate

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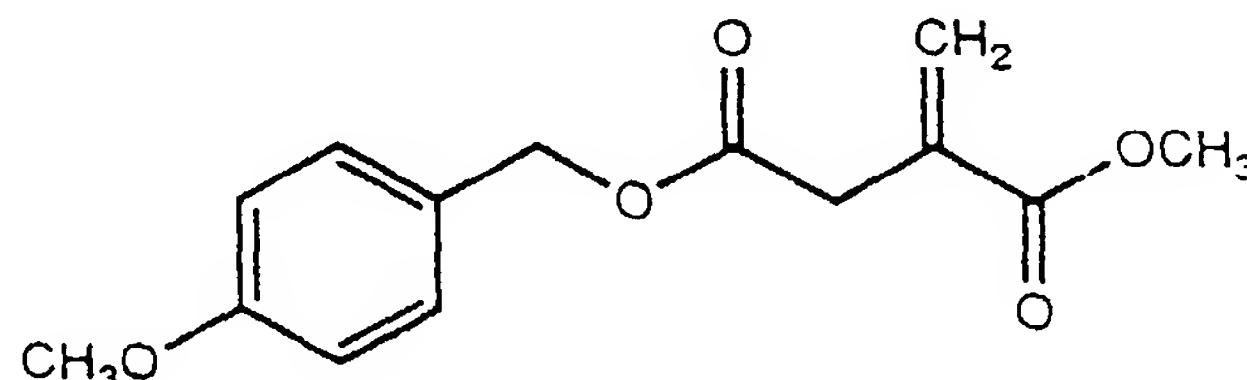


A 5 L three-necked round bottomed flask equipped with constant pressure addition funnel, reflux condenser, nitrogen inlet, and mechanical stirrer was charged with itaconic anhydride (660.8g, 5.88 mol) and toluene (2300 mL). The solution was warmed to reflux and treated with 4-methoxybenzyl alcohol (812.4g, 5.88 mol) dropwise over a 2.6h period. The solution was maintained at reflux for an additional 1.5h and then the contents were poured into three 2 L erlenmeyer flasks to crystallize. The solution was allowed to cool to room temperature whereupon the desired mono-ester crystallized. The product was isolated by filtration on a Buchner funnel and air dried to give 850.2g, 58% of material with mp 83-85°C, a second crop, 17% was isolated after cooling of the filtrate in an ice bath. ^1H NMR (CDCl_3) 300 MHz 7.32(d, $J=8.7$ Hz, 2H), 6.91(d, $J=8.7$ Hz, 2H), 6.49(s, 1H), 5.85(s, 1H), 5.12(s, 2H), 3.83(s, 3H), 3.40(s, 2H).

B. Preparation of Methyl 4(4-methoxybenzyl) itaconate

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A 5 L three-necked round bottomed flask equipped with reflux condenser, nitrogen inlet, constant pressure addition funnel and mechanical stirrer was charged with 4(4-methoxybenzyl) itaconate (453.4g, 1.81 mol) and created with 1,5-diazabicyclo[4.3.0]non-5-ene (275.6g, 1.81 mol), (DBN), dropwise so that the temperature did not rise above 15°C. To this stirring mixture was added a solution of methyl iodide (256.9g, 1.81 mol) in 250 mL of toluene from the dropping funnel over a 45m period. The solution was allowed to warm to room temperature and stirred for an additional 3.25h.

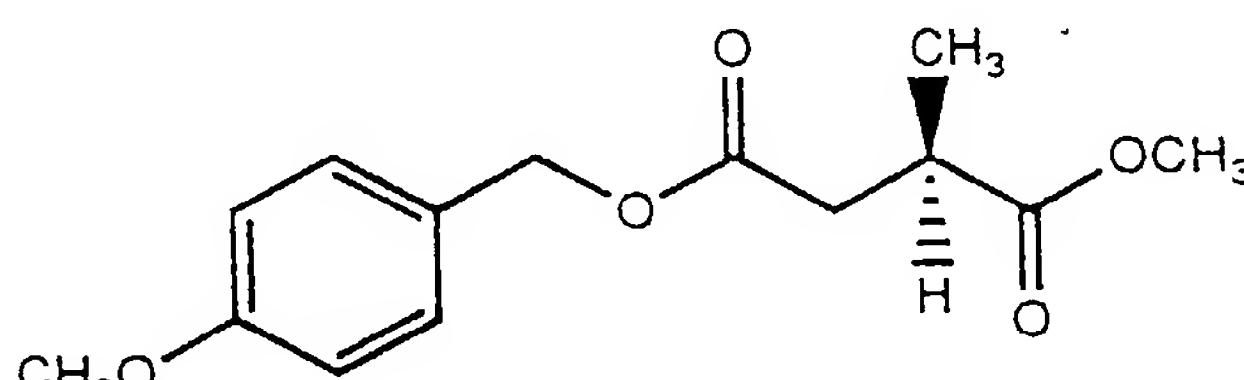
The precipitated DBN hydroiodide was removed by filtration, washed with toluene and the filtrate poured into a separatory funnel. The solution was washed with sat. aq. NaHCO_3 (2 X 500 mL), 0.2N HCl (1 X 500 mL), and brine (2 X 500 mL), dried over anhyd. MgSO_4 , filtered, and the solvent removed *in vacuo*. This gave a clear colorless oil, 450.2g, 94% whose NMR was consistent with the assigned structure. ^1H NMR (CDCl_3) 300 MHz 7.30(d, $J=8.7$ Hz, 2H), 6.90(d, $J=8.7$ Hz, 2H), 6.34(s, 1H), 5.71(s, 1H), 5.09(s, 2H), 3.82(s, 3H), 3.73(s, 3H), 3.38(s, 2H). ^{13}C NMR (CDCl_3) 170.46, 166.47, 159.51, 133.55, 129.97, 128.45, 127.72, 113.77, 66.36, 55.12, 51.94, 37.64.

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C. Preparation of Methyl 4(4-methoxybenzyl) 2(R)-methylsuccinate

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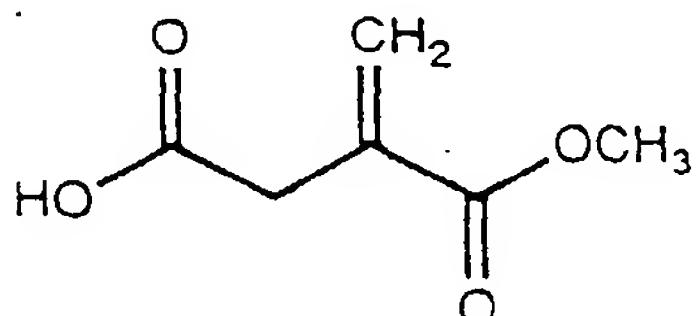
A 500 mL Fisher-Porter bottle was charged with methyl 4(4-methoxybenzyl) itaconate (71.1g, 0.269 mol), rhodium (R,R) DiPAMP catalyst (204mg, 0.269 mmol, 0.1 mol%) and degassed methanol (215 mL). The bottle was flushed 5

times with nitrogen and 5 times with hydrogen to a final pressure of 40 psig. The hydrogenation commenced immediately and after ca. 1h the uptake began to taper off, after 3h the hydrogen uptake ceased and the bottle was flushed with nitrogen, opened and the contents concentrated on a rotary evaporator to give a brown oil that was taken up in boiling *iso*-octane (ca. 200 mL, this was repeated twice), filtered through a pad of celite and the filtrate concentrated *in vacuo* to give 66.6g, 93% of a clear colorless oil, ¹H NMR (CDCl₃ 300 MHz 7.30(d, J=8.7 Hz, 2H), 6.91(d, J=8.7 Hz, 2H), 5.08(s, 2H), 3.82(s, 3H), 3.67(s, 3H), 2.95(ddq, J=5.7, 7.5, 8.7 Hz, 1H), 2.79(dd, J=8.1, 16.5 Hz, 1H), 2.45(dd, J=5.7, 16.5 Hz, 1H), 1.23(d, J=7.5 Hz, 3H).

D. Preparation of Methyl 2(R)-methylsuccinate

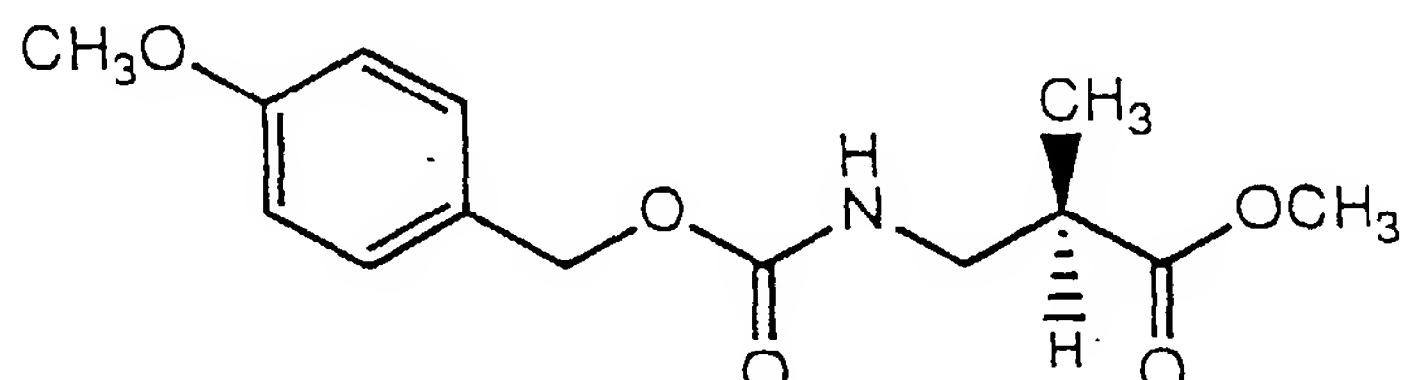
A 3 L three-necked round-bottomed flask equipped with a nitrogen inlet, mechanical stirrer, reflux condenser and constant pressure addition funnel was charged with methyl 4(4-methoxybenzyl) 2(R)-methylsuccinate (432.6g, 1.65 mol) and toluene (1200 mL). The stirrer was started and the solution treated with trifluoroacetic acid (600 mL) from the dropping funnel over 0.25h. The solution turned a deep purple color and the internal temperature rose to 45°C. After stirring for 2.25h the temperature was 27°C and the solution had acquired a pink color. The solution was concentrated on a rotary evaporator. The residue was diluted with water (2200 mL) and sat. aq. NaHCO₃ (1000 mL). Additional NaHCO₃ was added until the acid had been neutralized. The aqueous phase was extracted with ethyl acetate (2 X 1000 mL) to remove the by-products and the aqueous layer was acidified to pH=1.8 with conc. HCl. This solution was extracted with ethyl acetate (4 X 1000 mL), washed with brine, dried over anhyd. MgSO₄, filtered and concentrated on a rotary evaporator to give a colorless liquid 251g, >100% that was vacuum distilled through a short path apparatus cut 1: bath temperature 120°C @ >1mm, bp 25-29°C; cut 2: bath temperature 140°C @ 0.5mm, bp 95-108°C, 151g, [α]_d @ 25°C = +1.38°C (c=15.475, MeOH), [α]_d = +8.48°C (neat); cut 3: bath temperature 140°C, bp 108°C, 36g, [α]_d @ 25°C = +1.49°C (c=15.00, MeOH), [α]_d = +8.98°C (neat). Cuts 2 and 3 were combined to give 189g, 78% of product, ¹H NMR (CDCl₃) 300 MHz 11.6(brs, 1H), 3.72(s, 3H), 2.92(ddq, J=5.7, 6.9, 8.0 Hz, 1H), 2.81(dd, J=8.0, 16.8 Hz, 1H), 2.47(dd, J=5.7, 16.8 Hz, 1H), 1.26(d, J=6.9 Hz, 3H).

E. Preparation of Methyl Itaconate



A 50 mL round bottomed flask equipped with reflux condenser, nitrogen inlet and magnetic stir bar was charged with methyl 4(4-methoxybenzyl) itaconate (4.00g, 16 mmol), 12 mL of toluene and 6 mL of trifluoroacetic acid. The solution was kept at room temperature for 18 hours and then the volatiles were removed *in vacuo*. The residue was taken up in ethyl acetate and extracted three times with saturated aqueous sodium bicarbonate solution. The combined aqueous extract was acidified to pH=1 with aqueous potassium bisulfate and then extracted three times with ethyl acetate. The combined ethyl acetate solution was washed with saturated aqueous sodium chloride, dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo*. The residue was then vacuum distilled to give 1.23g, 75% of pure product, bp 85-87 @ 0.1 mm. ¹H NMR (CDCl₃) 300 MHz 6.34(s, 1H), 5.73(s, 2H), 3.76(s, 3H), 3.38(s, 2H). ¹³C NMR (CDCl₃) 177.03, 166.65, 129.220, 132.99, 52.27, 37.46.

F. Curtius Rearrangement of Methyl 2(R)-methylsuccinate: Preparation of Methyl N-Moz- α -methyl β -alanine.

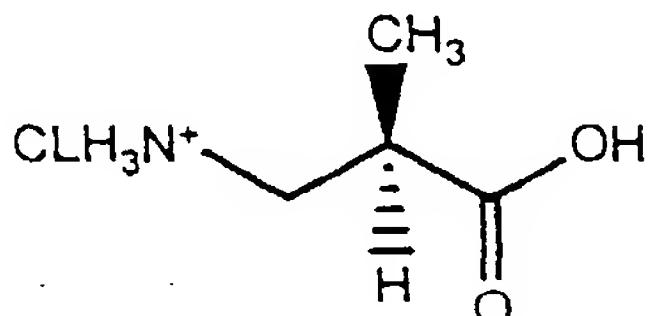


A 5L four necked round bottomed flask equipped with a nitrogen inlet, reflux condenser, mechanical stirrer, constant

pressure addition funnel, and thermometer adapter was charged with methyl 2(R)-methylsuccinate (184.1g, 1.26 mol), triethylamine (165.6g, 218 mL, 1.64 mol, 1.3 equivalents), and toluene (1063 mL). The solution was warmed to 85°C and then treated dropwise with a solution of diphenylphosphoryl azide (346.8g, 1.26 mol) over a period of 1.2h. The solution was maintained at that temperature for an additional 1.0h and then the mixture was treated with 4-methoxybenzyl alcohol (174.1g, 1.26 mol) over a 0.33h period from the dropping funnel. The solution was stirred at 88°C for an additional 2.25h and then cooled to room temperature. The contents of the flask were poured into a separatory funnel and washed with sat. aq. NaHCO₃ (2 X 500 mL), 0.2N HCl (2 X 500 mL), brine (1 X 500 mL), dried over anhyd. MgSO₄, filtered, and concentrated in vacuo to give 302.3g, 85% of the desired product as a slightly brown oil. ¹H NMR (CDCl₃) 300 MHz 7.32(d, J=8.4 Hz, 2H), 6.91(d, J=8.4 Hz, 2H), 5.2(brm, 1H), 5.05(s, 2H), 3.83(s, 3H), 3.70(s, 3H), 3.35(m, 2H), 2.70(m, 2H), 1.20(d, J=7.2 Hz, 3H).

G. Hydrolysis of Methyl N-Moz- α -methyl β -alanine: Preparation of α -methyl β -alanine Hydrochloride

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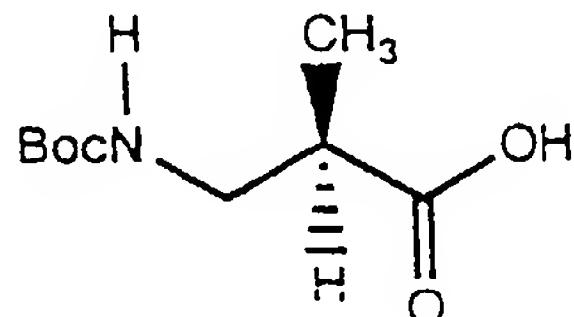


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A 5 L three-necked round bottomed flask equipped with a reflux condenser, nitrogen inlet and mechanical stirrer was charged with methyl N-Moz- α -methyl β -alanine (218.6g, 0.78 mol), glacial acetic acid (975 mL) and 12N hydrochloric acid (1960 mL). The solution was then heated to reflux for 3h. After the solution had cooled to room temperature (ca. 1h) the aqueous phase was decanted from organic residue (polymer) and the aqueous phase concentrated on a rotary evaporator. Upon addition of acetone to the concentrated residue a slightly yellow solid formed that was slurried with acetone and the white solid was isolated by filtration on a Buchner funnel. The last traces of acetone were removed by evacuation to give 97.7g, 90% of pure product, mp 128.5-130.5°C [α]_d @ 25°C=9.0°C (c=2.535, Methanol). ¹H NMR (D₂O) 300 MHz 3.29(dd, J=8.6, 13.0 Hz, 1H), 3.16(dd, J=5.0, 13.0m Hz, 1H), 2.94(ddq, J=7.2, 5.0, 8.6 Hz, 1H), 1.30(d,J=7.2 Hz, 3H); ¹³C NMR (D₂O) 180.84, 44.56, 40.27, 17.49.

H. Preparation of N-Boc α -Methyl β -Alanine

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A solution of α -methyl β -alanine hydrochloride (97.7g, 0.70 mol) in water (1050 mL) and dioxane (1050 mL) the pH was adjusted to 8.9 with 2.9N NaOH solution. This stirring solution was then treated with di-*tert*-butyl pyrocarbonate (183.3g, 0.84 mol, 1.2 equivalents) all at once. The pH of the solution was maintained between 8.7 and 9.0 by the periodic addition of 2.5N NaOH solution. After 2.5h the pH had stabilized and the reaction was judged to be complete. The solution was concentrated on a rotary evaporator (the temperature was maintained at <40°C). The excess di-*tert*-butyl pyrocarbonate was removed by extraction with dichloromethane and then the aqueous solution was acidified with cold 1N HCl and immediately extracted with ethyl acetate (4 X 1000 mL). The combined ethyl acetate extract was washed with brine, dried over anhyd. MgSO₄, filtered and concentrated on a rotary evaporator to give a thick oil 127.3g, 90% crude yield that was stirred with n-hexane whereupon crystals of pure product formed, 95.65g, 67%, mp 76-78°C, [α]_d @ 25°C=-11.8°C (c=2.4, EtOH). A second crop was obtained by concentration of the filtrate and dilution with hexane, 15.4g, for a combined yield of 111.05g, 78%. ¹H NMR (acetone D₆) 300 MHz 11.7 (brs, 1H), 6.05 (brs 1H), 3.35 (m, 1H), 3.22 (m, 1H), 2.50 (m, 1H), 1.45(s, 9H), 1.19 (d, J=7.3 Hz, 3H); ¹³C NMR (acetone D₆) 177.01, 79.28, 44.44, 40.92, 29.08, 15.50. Elemental analysis calc'd. for C₉H₁₇NO₄: C, 53.19, H, 8.42; N, 6.89. Found: C, 53.36; H, 8.46; N, 6.99.

I. Preparation of N-4-Methoxybenzyloxycarbonyl α -Methyl β -Alanine

A solution of N-4-methoxybenzyloxycarbonyl α -methyl β -alanine methyl ester (2.81g, 10.0 mmol) in 30 mL of 25% aqueous methanol was treated with lithium hydroxide (1.3 equivalents) at room temperature for a period of 2h. The 5 solution was concentrated in vacuo and the residue taken up in a mixture of water and ether and the phases separated and the organic phase discarded. The aqueous phase was acidified with aqueous potassium hydrogen sulfate to pH=1.5 and then extracted three times with ether. The combined ethereal phase was washed with saturated aqueous sodium chloride solution, dried over anhydrous magnesium sulfate, filtered and concentrated in vacuo to give 2.60 g, 10 97% of N-4-Methoxybenzyloxycarbonyl α -methyl β -alanine (N-Moz-AMBA) which was purified by recrystallization from a mixture of ethyl acetate and hexane to give 2.44g, 91% of pure product, mp 96-97°C, MH⁺=268. ¹H NMR (D₆-acetone/ 300 MHz) 1.16 (3H, d, J=7.2Hz), 2.70 (1H, m), 3.31 (2H, m), 3.31 (3H, s), 4.99 (2H, s), 6.92 (2H, 4, J=8.7 Hz), 7.13 (2H, d, J=8.7 Hz)-.

Example 8

Following generally the procedure of Example 7, the β -amino acids set forth in Table 1 were prepared.

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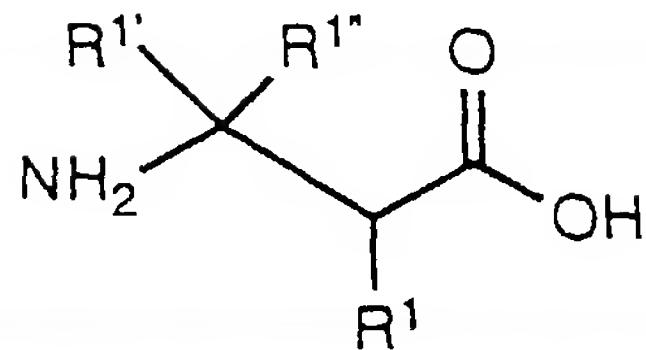
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Table 2

15	Entry	R ¹	R ^{1'}	R ^{1''}
20	1	-CH ₃	H	H
25	2	-CH(CH ₃) ₂	H	H
30	3	-C(CH ₃) ₃	H	H
35	4	H	H	H
40	5	H	-CH ₃	H
45	6	H	-CH ₃	-CH ₃
50	7	H	H	-CO ₂ CH ₃
55	8	H	H	-CONH ₂
60	9	-CH ₂ CH ₃	H	H
65	10	-CH ₂ CH(CH ₃) ₂	H	H
70	11	-CH ₂ C ₆ H ₅	H	H
75	12	-CH ₂ --OH	H	H
80	13	-CH ₂ -	H	H
85	14	-CH ₂ COOH	H	H
90	15	H	-CH(CH ₃) ₂	H
95	16	H	-CH ₂ CH(CH ₃) ₂	H
100	17	H	-CH ₂ -	H

Table 2 (Cont'd)

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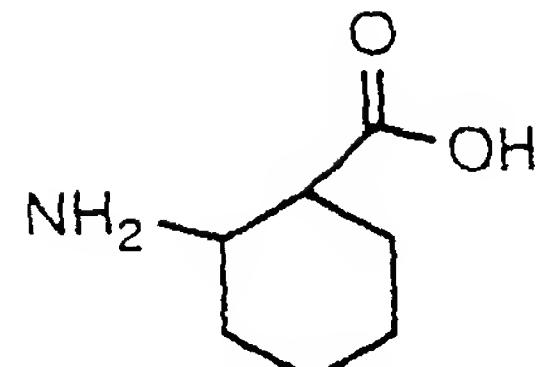
	Entry	R ¹	R ^{1'}	R ^{1''}
10	18	H	-CH ₂ CH ₂ -C ₆ H ₅	H
	19	H	- (CH ₂) ₃ -C ₆ H ₅	H
15	20	H	- (CH ₂) ₄ -C ₆ H ₅	H
	21	H	- (CH ₂) ₃ CH(C ₆ H ₅) ₂	H

Example 9

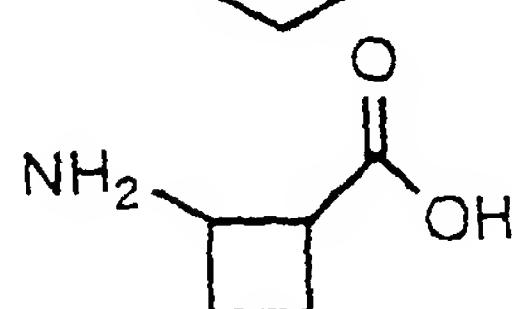
20

Utilizing generally the procedure set forth in Example 7, the following β -amino acid compounds were prepared.

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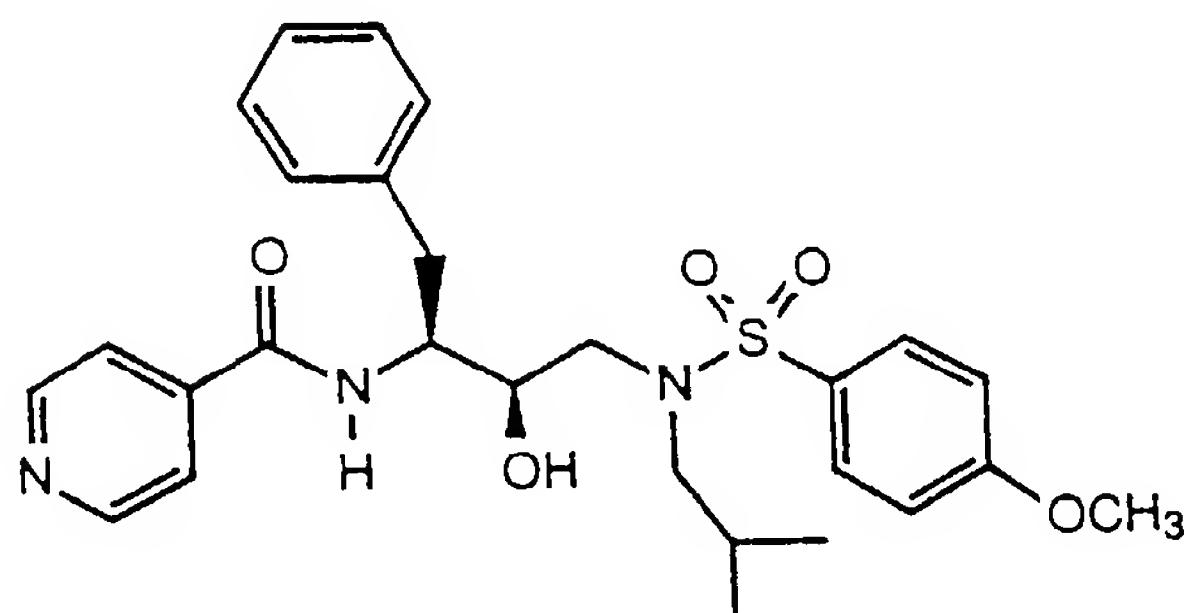
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Example 10A

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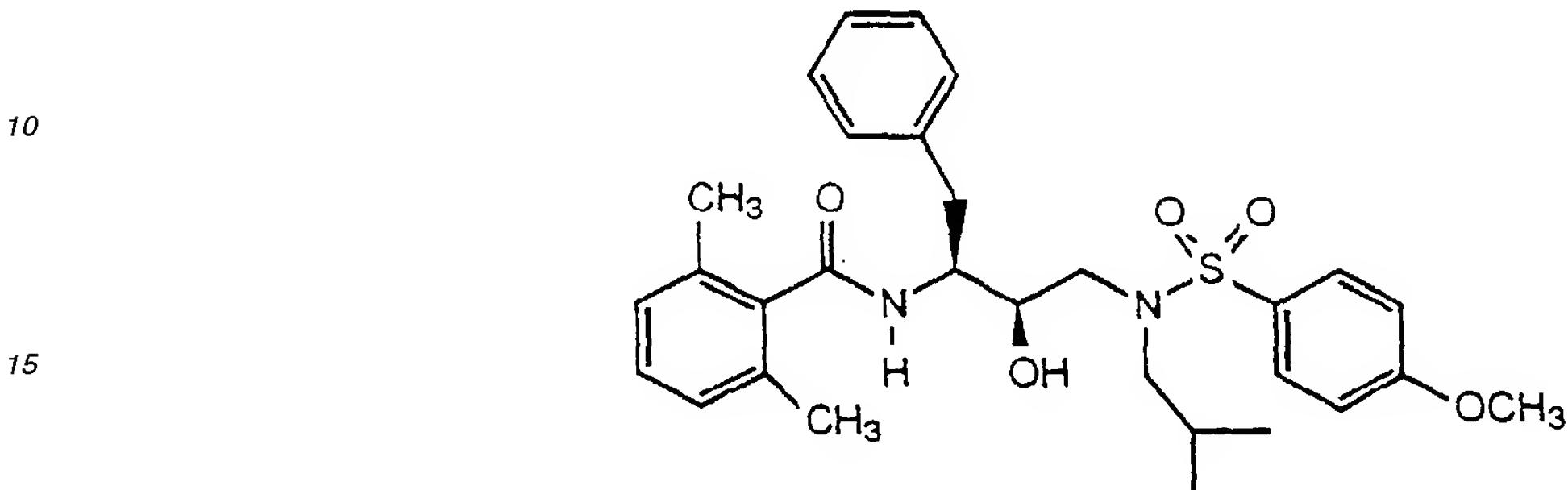
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Preparation of 4-Pyridinecarboxamide, N-[2R-hydroxy-3-[(4-methoxyphenyl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propyl]

To a solution of 231 mg (0.57 mmol) of 2R-hydroxy-3-[(2-methylpropyl)(4-methoxyphenyl)sulfonyl] amino-1S-(phenylmethyl)propylamine in 3 mL of methylene chloride at 0 °C, was added 288 mg(2.85 mmol) of triethylamine and then 112 mg(0.63 mmol) of isonicotinoyl chloride hydrochloride. After 19 hours at room temperature, the solvent was removed, ethyl acetate added, then washed with saturated sodium bicarbonate, brine, dried with magnesium sulfate,

filtered and concentrated to afford 290 mg of crude product. This was chromatographed on silica gel using 3-5% iso-propanol/methylene chloride as eluent to afford 190 mg of the desired compound; mass spectrum calc. for $C_{27}H_{34}N_3O_5S$ ($M + H$) 512.2219; found 512.2280.

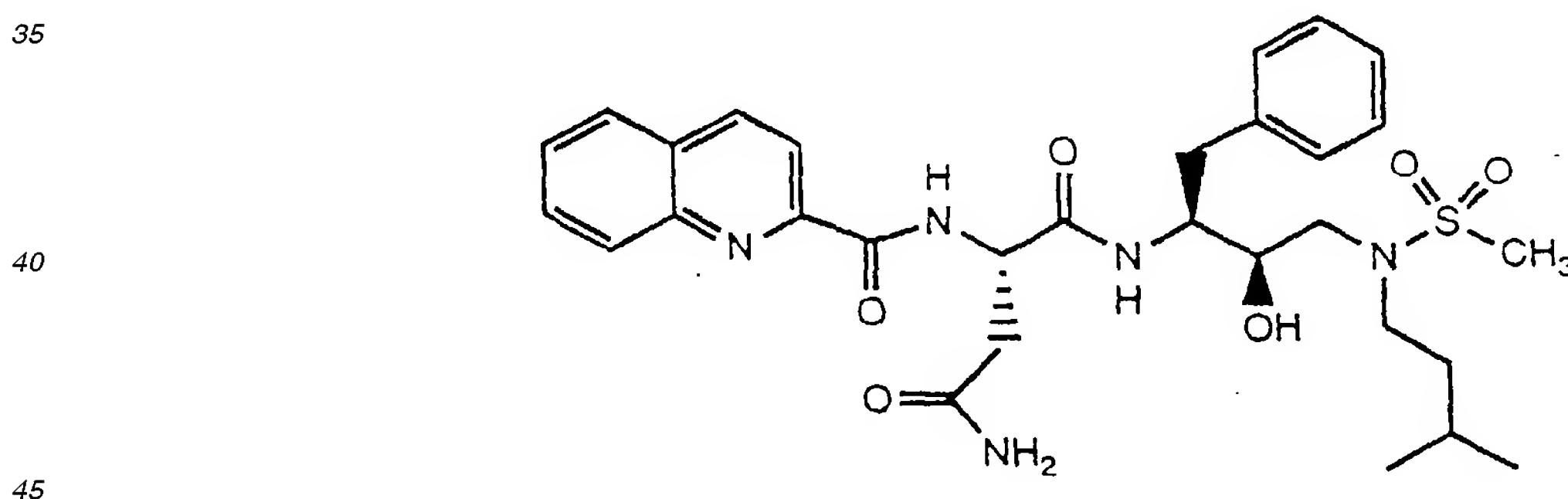
5 Example 10B



20 Preparation of Benzamide, N-[2R-hydroxy-3-[(4-methoxyphenyl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propyl]-2,6-dimethyl

To a solution of 83 mg (0.55 mmol) of 2,6-dimethylbenzoic acid and 125 mg (0.82 mmol) of N-hydroxybenzotriazole in 3 mL of anhydrous DMF at 0 °C was added 117 mg (0.61 mmol) of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride. After 2 hours at 0 °C, 203 mg (0.50 mmol) of 2R-hydroxy-3-[(2-methylpropyl)(4-methoxyphenyl)sulfonyl]amino-1S-(phenylmethyl)propylamine was added. After 22 hours at room temperature, the solvent was removed in vacuo, ethyl acetate added, then washed with saturated sodium bicarbonate, brine, dried over magnesium sulfate, filtered and concentrated to afford 300 mg of crude product. Chromatography on silica gel using 20-50% ethyl acetate/hexane afforded 37 mg of the desired product; mass spectrum calcd for $C_{30}H_{38}N_2O_5S$ ($M + H$) 539.2580; found 539.2632.

30 Example 11A



Preparation of N1-[2R-hydroxy-3-[(3-methylbutyl)(methylsulfonyl)amino]-1S-(phenylmethyl)propyl]-2S-[2-quinolinylcarbonyl]amino]butanediamide

50 Part A:

A solution of phenylmethyl [2R-hydroxy-3-[(3-methylbutyl)(methylsulfonyl)amino]-1S-(phenylmethyl)propyl]carbamate prepared as in Example 3A (100 mg) in methanol (10 mL) was hydrogenated over 10% palladium on carbon for 2 hours, filtered through diatomaceous earth and concentrated to give the product as an oil.

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Part B:

A solution of N-CBZ-L-asparagine (61 mg, 0.23 mmol) and N-hydroxybenzotriazole (33 mg, 0.22 mmol) in DMF

(2 mL) was cooled to 0° C with an ice bath and then EDC (42 mg, 0.22 mmol) was added. The solution was stirred for 30 minutes at 0° C and then the product of Part A (69 mg, 0.21 mmol) in DMF (2 mL) was added. After 30 minutes at 0° C the reaction was allowed to warm to room temperature and stir for 16 hours. The reaction mixture was then poured into a 50% saturated aqueous solution of sodium bicarbonate (100 mL) and the resulting white precipitate collected by suction filtration, washed with water and dried *in vacuo*. The phenylmethyl [3-amino-1S-[[2R-hydroxy-3-[(3-methylbutyl)(methylsulfonyl)amino]-1S-(phenylmethyl)amino]carbonyl]-3-oxopropyl]carbamate was obtained as a white solid Anal. Calcd. for $C_{28}H_{40}N_4O_7S$. 0.5 H₂O: C, 57.42; H, 7.06; N, 9.57. Found: C, 57.72; H, 7.21; N, 9.24.

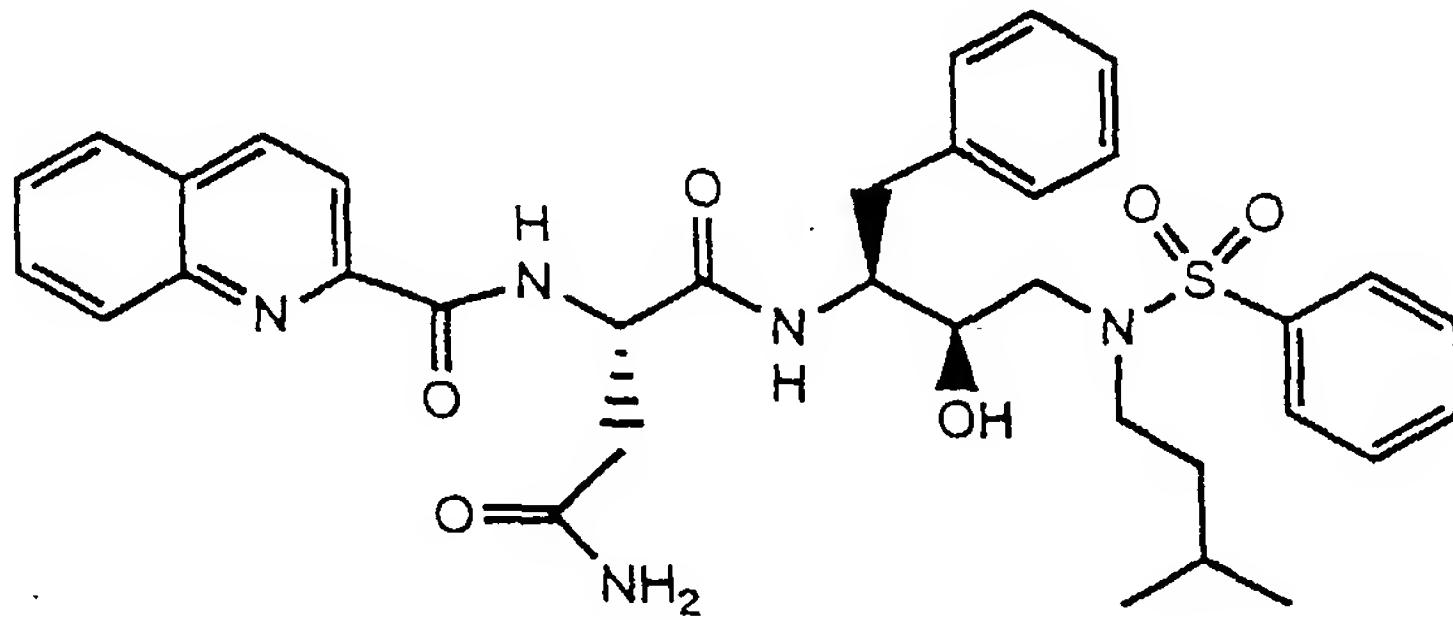
Part C:

A solution of phenylmethyl [3-amino-1S-[[2R-hydroxy-3-[(3-methylbutyl)(methylsulfonyl)amino]-1S-(phenylmethyl)amino]carbonyl]-3-oxopropyl]carbamate (135 mg, 0.23) in methanol (15 mL) was hydrogenated over 10% palladium on carbon for 6 hours, filtered through diatomaceous earth and concentrated to give the product as an oil.

Part D:

To a solution of the product from Part C (101 mg, 0.23 mmol) in DMF (5 mL) was added 2-quinoline carboxylic acid N-hydroxysuccinimide ester (67 mg, 0.25 mmol). The reaction was stirred at room temperature for 16 hours, then poured into a 50% saturated solution of sodium bicarbonate (60 mL). The resulting solid was collected by suction filtration washed with water and dried *in vacuo*. The N1-[2R-hydroxy-3-[(3-methylbutyl)(methylsulfonyl)amino]-1S-(phenylmethyl)propyl]-2S-[(2-quinolinylcarbonyl)amino]butanediamide was obtained as a white solid Anal. Calcd. for $C_{30}H_{39}N_5O_6S$. 0.1 H₂O: C, 58.52; H, 6.71; N, 11.37. Found: C, 58.34; H, 6.35; N, 11.13.

Example 11B



Preparation of N1-[2R-hydroxy-3-[(3-methylbutyl)(phenylsulfonyl)amino]-1S-(phenylmethyl)propyl]-2S-[(2-quinolinylcarbonyl)amino]butanediamide.

Part A:

The CBZ protected compound phenylmethyl [2R-hydroxy-3-[(3-methylbutyl)(phenylsulfonyl)amino]-1S-(phenylmethyl)propyl]carbamate (200 mg, 0.38 mmol) was deprotected by hydrogenation over 10% palladium on carbon and the resulting product obtained as an oil.

Part B:

The free amine from Part A was coupled with N-CBZ-L-asparagine (109 mg, 0.41 mmol) in the presence of N-hydroxybenzotriazole (63 mg, 0.41 mmol) and EDC (77 mg, 0.40 mmol) to give phenylmethyl [3-amino-1S-[[2R-hydroxy-3-[(3-methylbutyl)(phenylsulfonyl)amino]-1S-(phenylmethyl)amino]carbonyl]-3-oxopropyl]carbamate as a white solid Anal. Calcd. for $C_{33}H_{42}N_4O_7S$: C, 62.05; H, 6.63; N, 8.77. Found: C, 61.86; H, 6.60; N, 8.64.

Part C:

The product of Part B (110 mg, 0.17) was deprotected by hydrogenation over 10% palladium on carbon to give the product as an oil.

Part D:

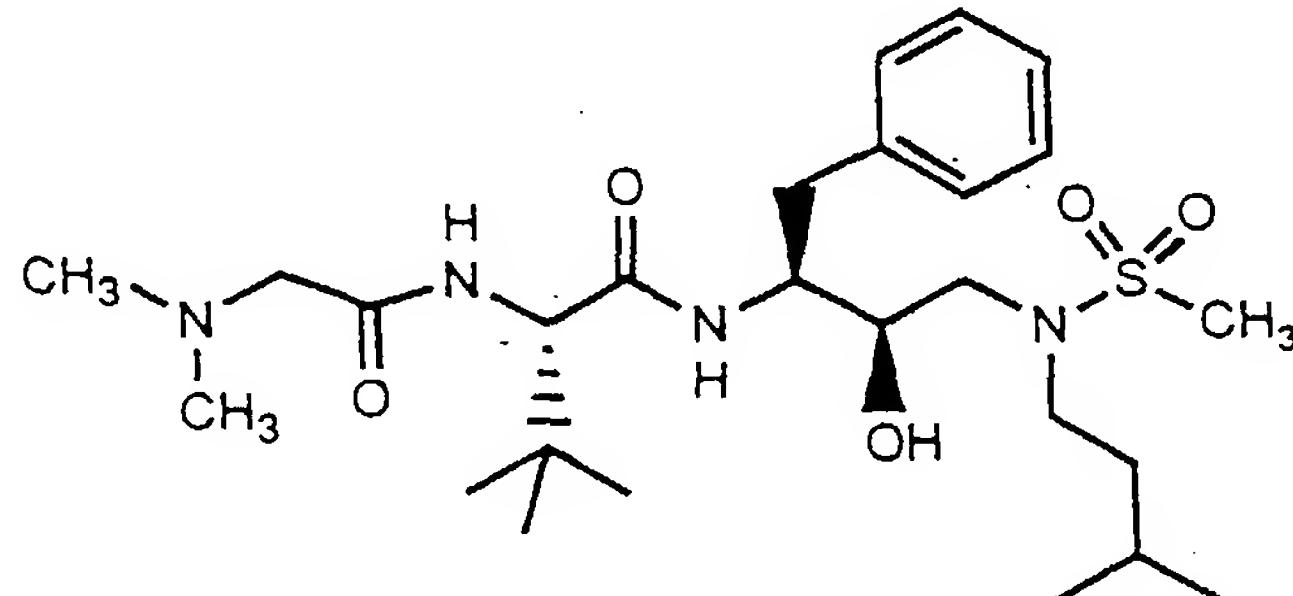
The resulting free amine was coupled with 2-quinoline carboxylic acid N-hydroxysuccinimide ester (45 mg, 0.17 mmol) to give N1- [2R-hydroxy-3-[(3-methylbutyl)(phenylsulfonyl)amino]-1S-(phenylmethyl)propyl]-2S-[(2-quinolinyl-carbonyl)amino]butanediamide as a white solid Anal. Calcd. for $C_{35}H_{41}N_5O_6S$: C, 63.71; H, 6.26; N, 10.61. Found: C, 63.59; H, 6.42; N, 10.42.

Example 12A

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Preparation of 2S-[(dimethylamino)acetyl]amino-N-[2R-hydroxy-3-[(3-methylbutyl)(methylsulfonyl)amino]-1S-(phenylmethyl)propyl]-3,3-dimethylbutanamide

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Part A:

To a solution of N-CBZ-L-tert-leucine (100 mg, 0.38 mmol) and N-hydroxybenzotriazole (52 mg, 0.34 mmol) in DMF (3 mL) was added EDC (65 mg, 0.34 mmol). The solution was stirred for 60 minutes at room temperature and then the product of Example 10, Part A (105 mg, 0.32 mmol) in DMF (2 mL) was added. The reaction was stirred for 16 hours at room temperature, then poured into a 50% saturated solution of sodium bicarbonate (50 mL). The aqueous mixture was extracted twice with ethyl acetate (25 mL). The combined ethyl acetate layers were washed with water (25 mL) and dried over magnesium sulfate. Filtration and concentration produced an oil which was chromatographed on silica gel (50 gm) eluting with 2.5 % methanol in dichloromethane. The phenylmethyl [1S-[[2R-hydroxy-3-[(3-methylbutyl)-(methylsulfonyl)amino]-1S-(phenylmethyl)propyl]amino]-carbonyl]-2,2-dimethylpropyl]carbamate was obtained as a gummy solid Anal. Calcd. for $C_{30}H_{45}N_3O_6S \Delta 2.2 H_2O$: C, 58.55; H, 8.09; N, 6.83. Found: C, 58.38; H, 7.77; N, 7.10.

40

A solution of phenylmethyl [IS-[[[2R-hydroxy-3-[(3-methylbutyl) (methylsulfonyl)amino]-1S-(phenylmethyl)propyl]amino]carbonyl]-2,2-dimethylpropyl]carbamate (100 mg, 0.17 mmol) in methanol (10 mL) was hydrogenated over 10% palladium on carbon for 2 hours. The reaction was filtered through diatomaceous earth and concentrated to an oil.

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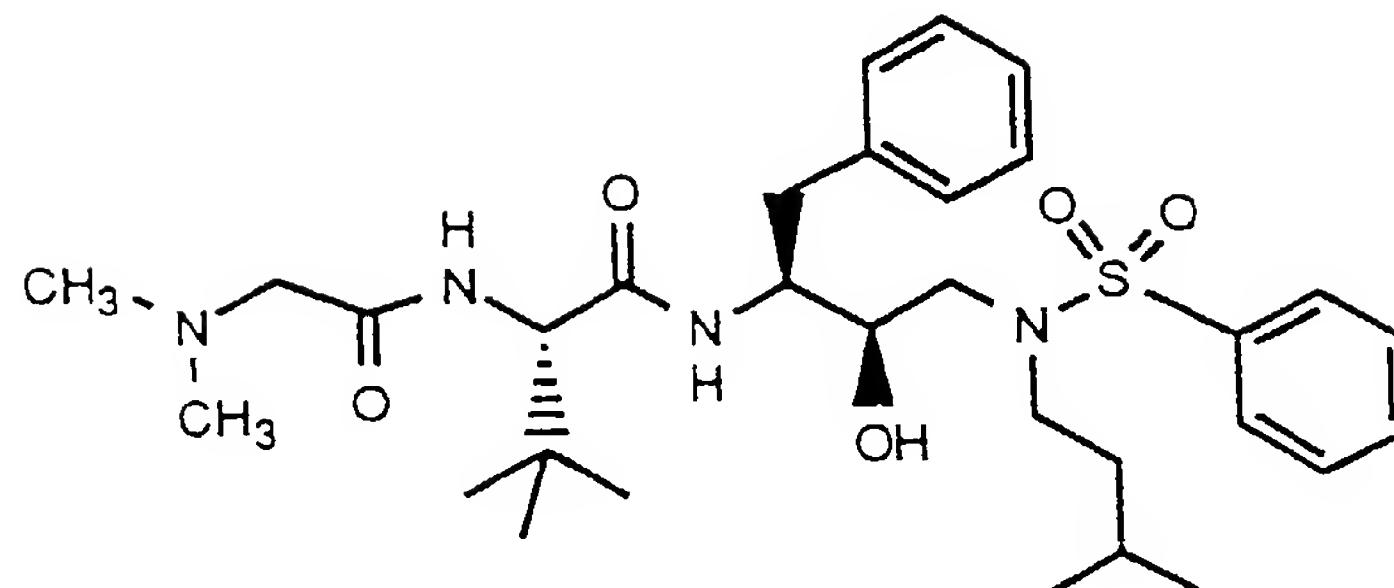
Part C:

N,N-dimethylglycine (20 mg, 0.19 mmol), N-hydroxybenzotriazole (28 mg, 0.18 mmol) and EDC (35 mg, 0.18 mmol) were stirred in DMF (4 mL) at room temperature for 40 minutes. The product from Part B in DMF (4 mL) was added and the reaction mixture stirred for 16 hours, then poured into a 50% saturated sodium bicarbonate solution (50 mL). The aqueous mixture was extracted three times with dichloromethane (30 mL) which in turn were washed with water (30 mL) and dried over magnesium sulfate. Filtration and concentration afforded an oil. The oil was chromatographed on silica gel (50 gm) eluting initially with 2.5 % methanol in dichloromethane (400 mL) and then with 5% methanol in dichloromethane. The 2S-[(dimethylamino)acetyl]amino-N-[2R-hydroxy-3-[(3-methylbutyl)(methylsulfonyl)amino]-1S-(phenylmethyl)-propyl]-3,3-dimethylbutanamide was obtained as a white solid Anal. Calcd. for $C_{26}H_{46}N_4O_5S \Delta 0.5 CH_2Cl_2$: C, 56.04; H, 8.34; N, 9.87. Found: C, 56.06; H, 8.36; N, 9.70.

Example 12B

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15 Preparation of 2S-[[[(dimethylamino)acetyl]amino]-N-[2R-hydroxy-3-[(3-methylbutyl)(phenylsulfonyl)amino]-1S-(phenylmethyl)propyl]-3,3-dimethylbutaneamide

Part A:

20 To a solution of N-CBZ-L-tert-leucine (450 mg, 1.7 mmol) and N-hydroxybenzotriazole (260 mg, 1.7 mmol) in DMF (10 mL) was added EDC (307 mg, 1.6 mmol). The solution was stirred for 60 minutes at room temperature and then the product of Example 11, Part A (585 mg, 1.5 mmol) in DMF (2 mL) was added. The reaction was stirred for 16 hours at room temperature, then poured into a 50% saturated solution of sodium bicarbonate (200 mL). The aqueous mixture was extracted thrice with ethyl acetate (50 mL). The combined ethyl acetate layers were washed with water (50 mL) and saturated NaCl solution (50 mL), then dried over magnesium sulfate. Filtration and concentration produced an oil which was chromatographed on silica gel (50 gm) eluting with 20% ethyl acetate in hexane. The phenylmethyl [1S-[[2R-hydroxy-3-[(3-methylbutyl)(phenylsulfonyl)amino]-1S-(phenylmethyl)propyl]amino]carbonyl]-2,2-dimethylpropyl carbamate was obtained as a solid Anal. Calcd for $C_{35}H_{47}N_3O_6S$: C, 65.91; H, 7.43; N, 6.59. Found: C, 65.42; H, 7.24; N, 6.55.

30

Part B:

35 A solution of phenylmethyl [1S-[[[2R-hydroxy-3-[(3-methylbutyl)(phenylsulfonyl)amino]-1S-(phenylmethyl)propyl]amino]carbonyl]-2,2-dimethylpropyl carbamate (200 mg, 0.31 mmol) in methanol (15 mL) was hydrogenated over 10% palladium on carbon for 2 hours. The reaction was filtered through diatomaceous earth and concentrated to an oil.

Part C:

40 The resulting free amine from part B (150 mg, 0.3 mmol) was combined with diisopropylethylamine (114 uL, 0.33 mmol) in dichloromethane (5 mL). To this was added bromoacetyl chloride (27 uL, 0.33 mmol) dropwise. The reaction was stirred for 30 minutes at room temperature, then diluted with dichloromethane (30 mL) and extracted with 1 N HCl, water, and then saturated NaCl solution (25 mL each). The organic solution was dried over $MgSO_4$ and concentrated to a solid. The 2S-[[bromoacetyl]amino]-N-[2R-hydroxy-3-[(3-methylbutyl)(phenylsulfonyl)amino]-1S-(phenylmethyl)propyl]-3,3-dimethylbutaneamide was sufficiently pure for use in the next step. This material can also be prepared by substituting bromoacetic anhydride for bromoacetyl chloride, or one can use chloroacetyl chloride or chloroacetic anhydride.

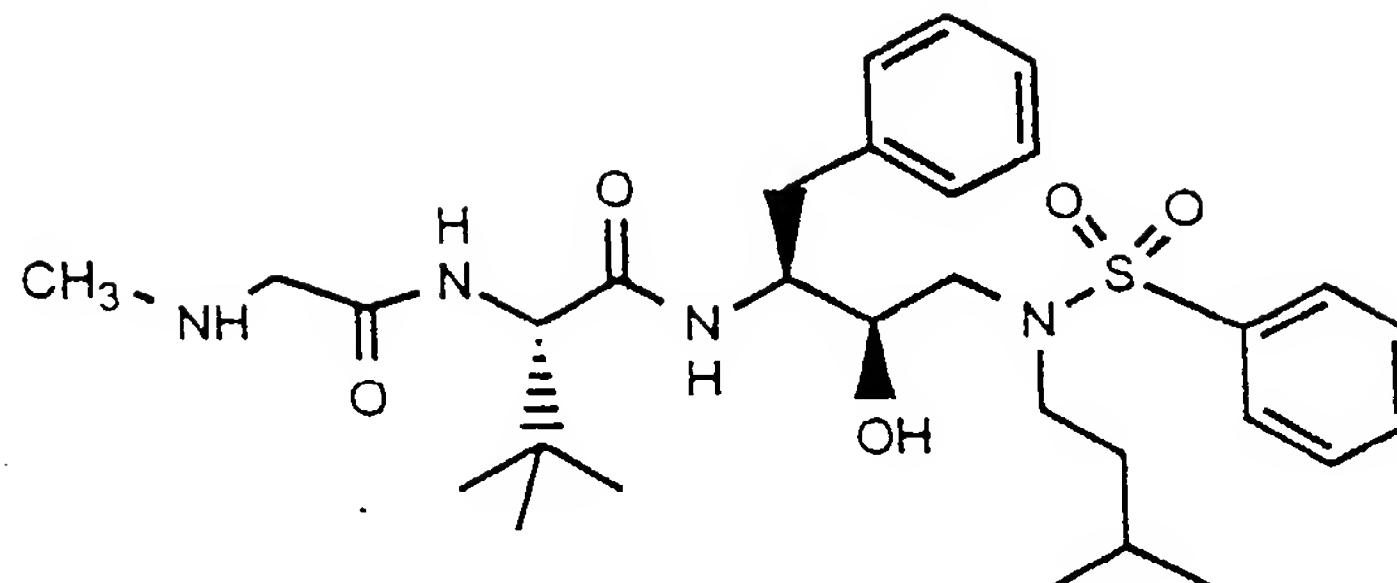
Part D:

50 The product from part C was dissolved in dichloromethane (5 mL) and diisopropylethylamine (114 uL, 0.66 mmol) and dimethylamine hydrochloride (53 mg, 0.66 mmol) were added. The reaction was stirred for 18 hours then concentrated under a stream of nitrogen to about 1 mL. The residue was chromatographed on silica gel (50 gm) using 2% methanol in dichloromethane. The 2S-[[[(dimethylamino)acetyl]amino]-N-[2R-hydroxy-3-[(3-methylbutyl)(phenylsulfonyl)amino]-1S-(phenylmethyl)propyl]-3,3-dimethylbutaneamide was obtained as a solid. Anal. Calcd for $C_{31}H_{48}N_4O_5S$: C, 63.24; H, 8.22; N, 9.52. Found: C, 63.03; H, 8.01; N, 9.40.

Example 12C

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15 Preparation of 2S-[(methylamino)acetyl]amino-N-[2R-hydroxy-3-[(3-methylbutyl)(phenylsulfonyl)amino]-1S-(phenylmethyl)propyl]-3,3-dimethylbutaneamide

2S-[[bromoacetyl]amino]-N-[2R-hydroxy-3-[(3-methylbutyl)(phenylsulfonyl)amino]-1S-(phenylmethyl)propyl]-3,3-dimethylbutaneamide (103 mg, 0.16 mmol) and 40% aqueous methylamine (42 uL, 0.49 mmol) were combined in ethanol (2 mL) and stirred at room temperature for 24 hours. The reaction mixture was concentrated to dryness and triturated with ether. The solid material was removed by filtration and the filtrate concentrated to an oil. The oil was chromatographed on silica (50 gm) using 4% methanol in dichloromethane. The 2S-[(methylamino)acetyl]amino-N-[2R-hydroxy-3-[(3-methylbutyl)(phenylsulfonyl)amino]-1S-(phenylmethyl)propyl]-3,3-dimethylbutaneamide was obtained as a solid. Anal. Calcd for C₃₀H₄₆N₄O₅S: C, 62.69; H, 8.07; N, 9.75. Found: C, 62.38; H, 8.14; N, 9.60.

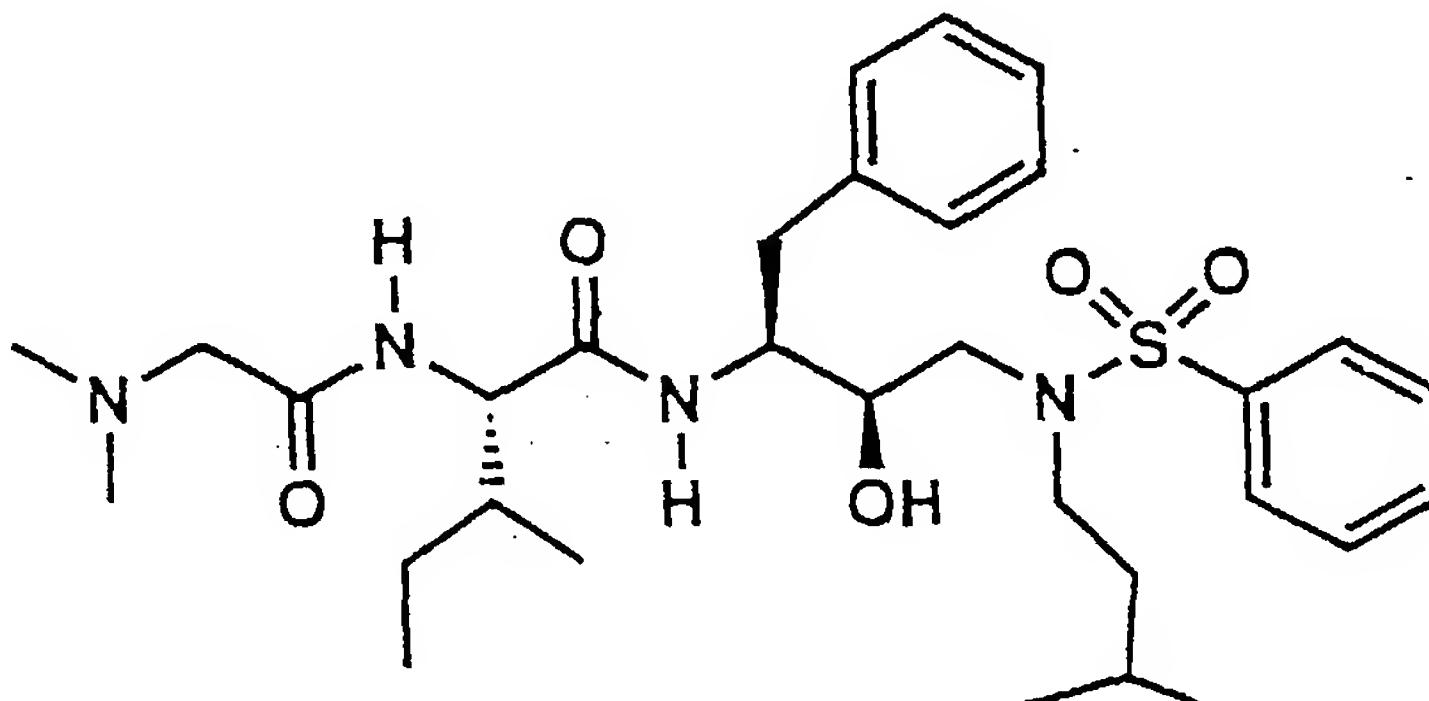
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Example 12D

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Preparation of Pentanamide, 2S-[(Dimethylamino)acetyl]amino-N-[2R-hydroxy-3-[(3-methylbutyl)phenylsulfonyl]amino]-1S-(phenylmethyl)propyl]-3S-methyl-45 Part A:

To a solution the amine product of Example 11, Part A; (2.79 g, 7.1 mmol) in 27 mL of dioxane was added (2.3 g, 7.1 mmol) of N-t-butylcarbonyl-L-isoleucine-N-hydroxysuccinamide ester, and the reaction was stirred under nitrogen atmosphere for 16 hours. The contents of the reaction were concentrated in vacuo, and the residue dissolved in ethyl acetate, washed with potassium hydrogen sulfate (5% aqueous), saturated sodium bicarbonate, and saturated sodium chloride. The organic layer was dried over magnesium sulfate, filtered and concentrated to yield 4.3 grams of crude material which was chromatographed using 3:1 ethyl acetate: hexane to obtain 3.05g, 72% yield of Pentanamide, 2S-[(1,1-dimethylethoxy)carbonyl]amino]-N-[2R-hydroxy-3-[(3-methylbutyl)phenylsulfonyl]amino]-1S-(phenylmethyl)propyl]-3-methyl-.

55

Part B

(3.05g, 5.0 mmol) of the product from Part A; was dissolved in 20 mL of 4N HCl in dioxane and stirred under

nitrogen atmosphere for 1.5 hours. The contents were concentrated in vacuo, and chased with diethyl ether. The crude hydrochloride salt was pumped on-at 1 mm Hg until dry to yield 2.54 g of product as its hydrochloride salt.

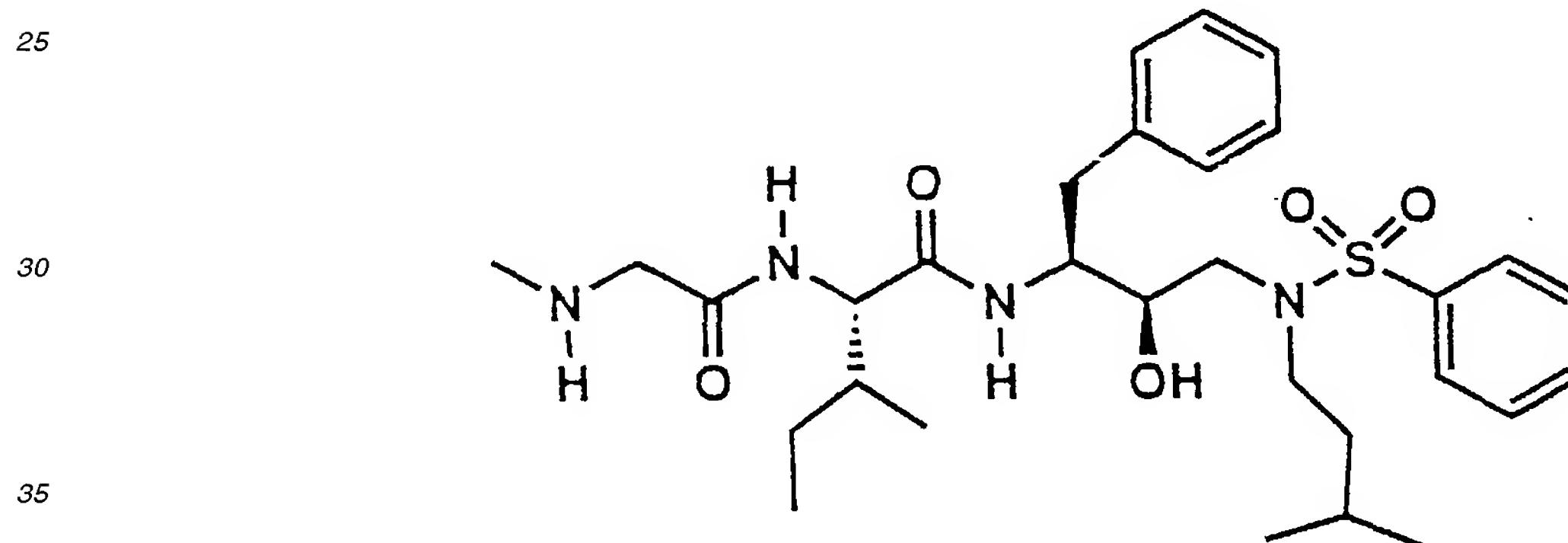
Part C:

(2.54 g, 5.0 mmol) of amine hydrochloride was dissolved in 50 mL of tetrahydrofuran and to this was added (1.01 g, 10 mmol) of 4-methyl-morpholine, at which time a precipitate forms. To this suspension was added chloroacetic anhydride (0.865 g, 5.0 mmol) and stirred for 40 minutes. The contents were concentrated in vacuo, and the residue partitioned in ethyl acetate (200 mL) and 5% KHSO₄. The organic layer was washed with saturated sodium bicarbonate, and saturated sodium chloride, dried over magnesium sulfate, filtered and concentrated to yield the crude product. Purification by silica gel chromatography using an eluant of 1:1 ethyl acetate; hexanes yielded 1.89 grams of pure chloroacetamide.

Part D:

To a solution of chloroacetamide (1.89 g, 3.2 mmol) from Part C, in 25 mL of tetrahydrofuran was added 4.0 mL of 50% aqueous dimethylamine and the solution was stirred for 1 hour. The solution was concentrated in vacuo and the residue was dissolved in ethyl acetate and washed with water. The organic layer was dried over magnesium sulfate, filtered and concentrated to yield the crude product which was purified by crystallization from ethyl acetate and isooc-tane to yield 1.80 g, (88% yield), mp. = 121-122 C, HRes. MS. calc. 589.3424, found 589.3405.

Example 12E



Preparation of Pentanamide, 2S-[[(Methylamino)acetyl]amino]-N-[2R-hydroxy-3-[(3-methylbutyl)(phenylsulfonyl)amino]-1S-(phenylmethyl)propyl]-3S-methyl-

40 To a solution of the chloroacetamide of Example 12D, Part C, (2.36 g, 4.0 mmol) in tetrahydrofuran (25 mL) was added 3 mL of aqueous methylamine 40 wt%, and the reaction stirred for 1 hour. The contents were concentrated and the residue was partitioned between ethyl acetate (100 mL) and water (100 mL). The organic layer was dried over magnesium sulfate, filtered and concentrated to yield the crude product, which was purified by recrystallization from ethyl acetate heptane; (M+H)575, HRes. found 575.3267.

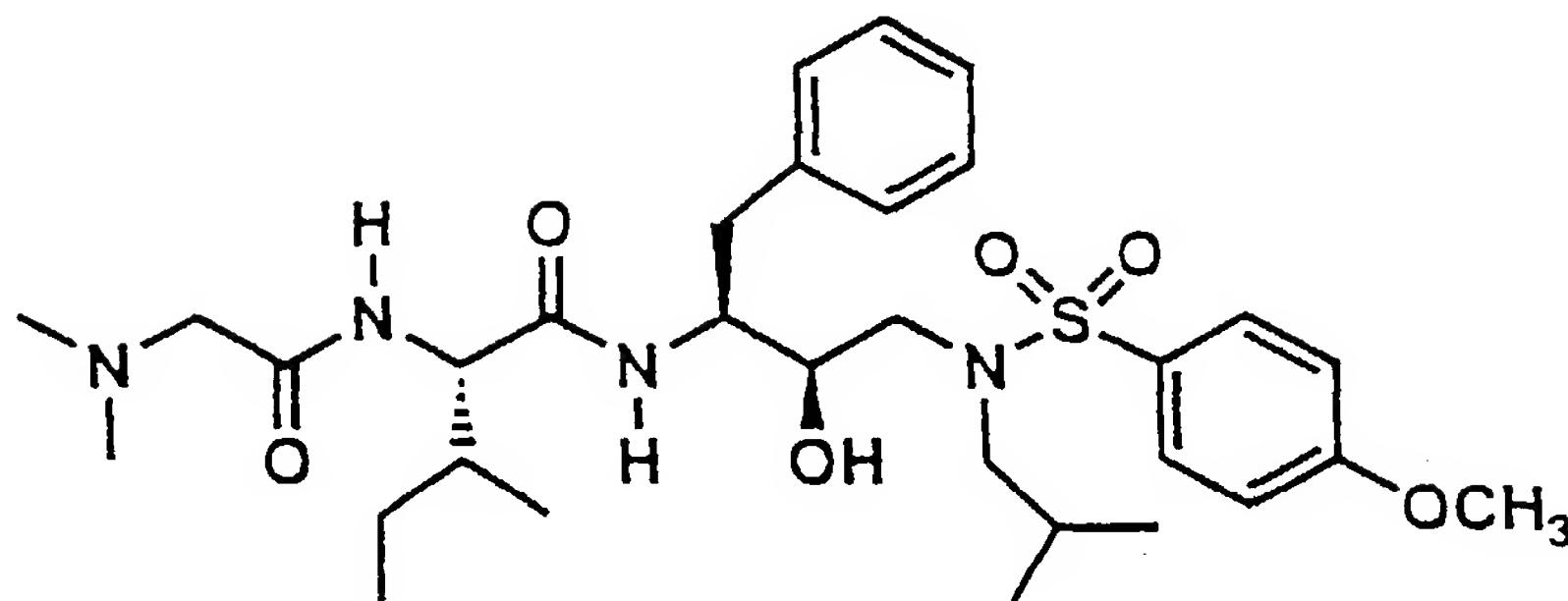
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Example 12F

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Preparation of Pentanamide, 2S-[(Dimethylamino)acetyl]amino-N-[2R-hydroxy-3-[(3-methylpropyl)(4-methoxyphenylsulfonyl)amino]-1S-(phenylmethyl)propyl]-3S-methyl-

Part A:

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To a solution of 2R-hydroxy-3-[(2-methylpropyl)(4-methoxyphenylsulfonyl)amino]1-S-propylamine (1.70 g, 4.18 mmol) in 40 mL of dichloromethane was added N-carbobenzyloxy-L-isoleucine-N-hydroxysuccinamide ester (1.51 g, 4.18 mmol) and the solution stirred under nitrogen atmosphere for 16 hours. The contents were concentrated in vacuo and the residue was redissolved in ethyl acetate. The ethyl acetate solution was washed with an aqueous solution of 5% KHSO₄, saturated sodium bicarbonate, and saturated sodium chloride, dried over magnesium sulfate, filtered, and concentrated to yield 2.47g of crude product. The product was purified by silica gel chromatography using 1 2:1 hexane: ethyl acetate eluant to yield 2.3 g. (84% yield) of Pentanamide, 2-[(carbobenzyloxy)amino]-N-[2-hydroxy-3-[(3-methylpropyl)(4-methoxyphenylsulfonyl)amino]-1-(phenylmethyl)propyl]-3-methyl-, [4-(R*,S*,S*)].

Part B:

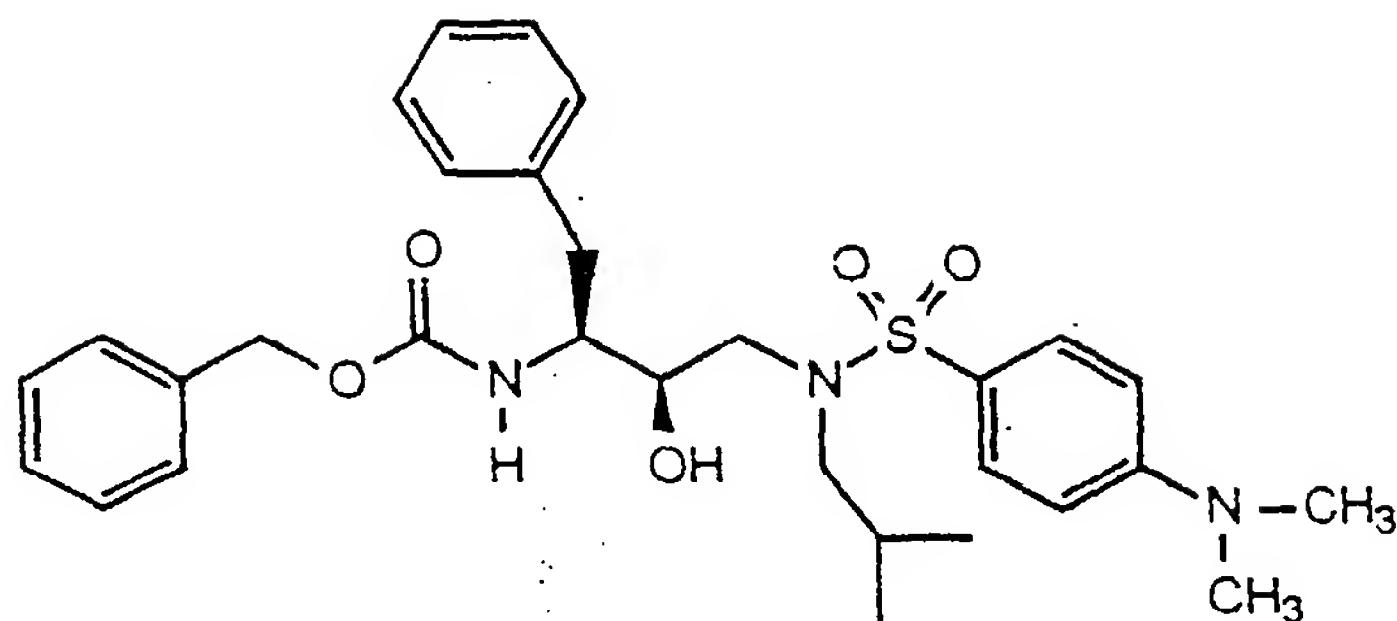
(1.18 g, 1.8 mmol) of the product from Part A was dissolved in 50 mL of methanol, and to this was added 250 mg of 10% Palladium on Carbon while under a stream of nitrogen. The suspension was hydrogenated using 50 psig of hydrogen for 20 hours. The contents were purged with nitrogen and filtered through celite, and concentrated in vacuo to yield 935 mg of Pentanamide, 2S-(amino)-N-[2R-hydroxy-3-[(3-methylpropyl)(4-methoxyphenylsulfonyl)amino]-1-S-(phenylmethyl)propyl]-3S-methyl-, which was used without further purification.

Part C:

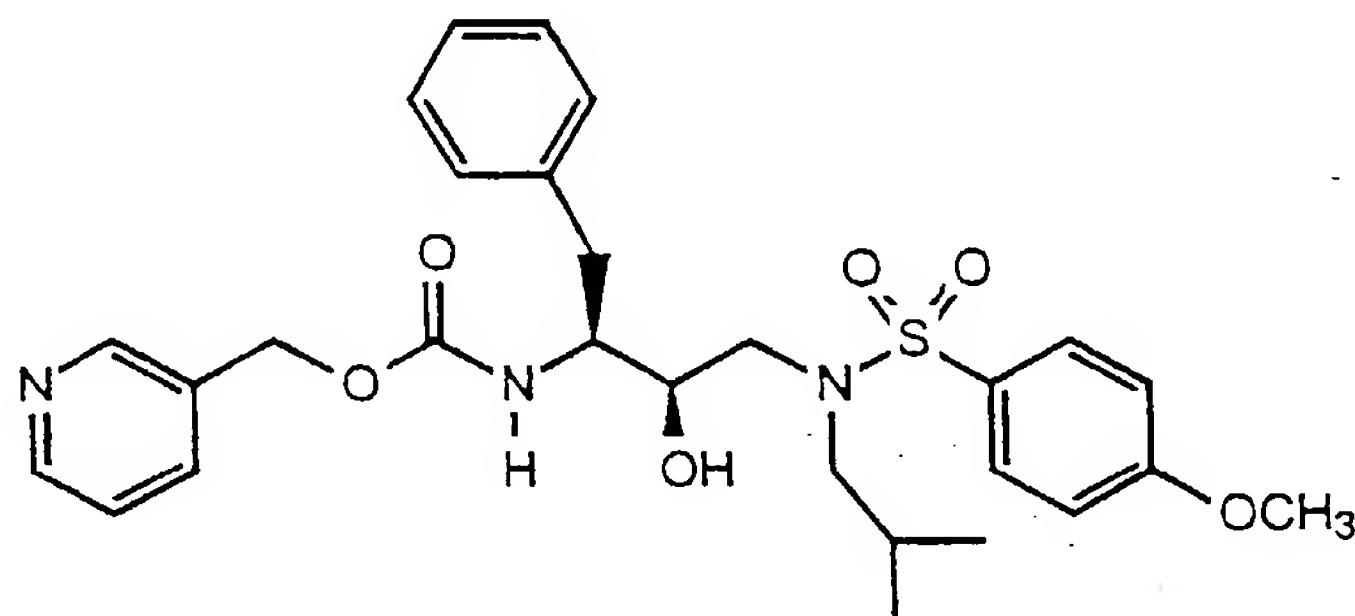
(0.935 g, 1.8 mmol) of the amine from Part B was dissolved in 15 mL of dioxane and to this was added (190 mg, 1.85 mmol) of 4-methylmorpholine followed by (0.315 g, 1.8 mmol) of chloroacetic anhydride. The reaction mixture was stirred under nitrogen atmosphere for 3 hours, concentrated in vacuo, and redissolved in ethyl acetate. The ethyl acetate solution was washed with 50 mL of 5% aqueous KHSO₄, saturated NaHCO₃, and saturated NaCl solution, dried over MgSO₄, filtered and concentrated to yield 613 mg, (68% yield) of Pentanamide, 2S-[(chloroacetyl)amino]-N-[2R-hydroxy-3-[(3-methylpropyl)(4-methoxyphenylsulfonyl)amino]-1S-(phenylmethyl)propyl]-3S-methyl-, after purification by silica gel chromatography using 1:1 hexane:ethyl acetate.

Part D:

To a solution of the chloroacetamide from Part C; (673 mg, 1.10 mmol) in 20 mL of tetrahydrofuran was added 5 mL of 50 wt% aqueous dimethylamine and the solution was stirred for 1 hour. The reaction was concentrated and the residue was redissolved in 50 mL of ethyl acetate and washed with 25 mL of water. The ethyl acetate layer was dried over magnesium sulfate, filtered and concentrated to yield a crude solid which was purified by silica gel column chromatography using an eluant of 97:3 dichloromethane:methanol to provide 400 mg of Pentanamide, 2S-[(Dimethylamino)acetyl]amino-N-[2R-hydroxy-3-[(3-methylpropyl)(4-methoxyphenylsulfonyl)amino]-1S-(phenylmethyl)propyl]-3S-methyl-.

Example 13APreparation of Carbamic acid, [2R-hydroxy-3-[(4-dimethylaminophenyl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propyl-, phenylmethyl ester

20 To a solution of 100mg (0.19 mmol) of carbamic acid, [2R-hydroxy-3-[(4-fluorophenyl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propyl-, phenylmethyl ester in 1 mL of pyridine was added 53 μ L of triethylamine and 120 μ L (p.95 mmol) of 40% aqueous dimethylamine. After heating for 24 hours at 100 C, the solution was cooled, ethyl acetate added, then washed with 5% citric acid, saturated sodium bicarbonate, dried over magnesium sulfate, filtered and concentrated. The resulting solid was recrystallized from ethyl acetate/hexane to afford 10 mg of the desired product; mass spectrum m/e = 540 (M+H).

Example 13BPreparation of Carbamic acid, [2R-hydroxy-3-[(4-methoxyphenyl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propyl-, 3-pyridylmethyl esterPart A:

45 A solution of N-benzyloxycarbonyl-3S-amino-1,2-S-epoxy-4-phenylbutane (50g, 0.168 mol) and isobutylamine (246g, 3.24 mol) in 650 mL of isopropyl alcohol was refluxed for 1.25 hours. The solution was cooled to room temperature, concentrated in vacuo and then poured into 1L of stirring hexane whereupon the product crystallized from solution, was collected and air dried to give 57.6 g of N-[3S-benzyloxycarbonylamino-2R-hydroxy-4-phenyl]-N-isobutylamine, mp 108-109.5 C, mass spectrum m/e=371(M+H).

Part B:

55 The amine from part A (1.11g, 3.0 mmol) and triethylamine (324mg, 3.20 mmol) in 20 mL of methylene chloride was treated with 715 mg(3.46 mmol) of 4-methoxybenzenesulfonyl chloride. The solution was stirred at room temperature for 6 hours, concentrated, dissolved in ethyl acetate, then washed with 1N potassium hydrogen sulfate, saturated sodium bicarbonate, brine, dried over magnesium sulfate, filtered and concentrated to afford a clear oil. This was recrystallized from diethyl ether to afford 1.27 g of carbamic acid, [2R-hydroxy-3-[(4-methoxyphenyl)sulfonyl](2-meth-

ylpropyl)amino]-1S-(phenylmethyl)propyl]-, phenylmethyl ester, mp 97-101 C, mass spectrum m/e=541 (M+H).

Part C:

5 A solution of 930mg (3.20 mmol) of the product of part B in 30 mL of methanol was hydrogenated in the presence
of 70 mg of a 10% palladium on carbon catalyst under 40 psig for 17 hours, the catalyst was removed by filtration, and
the solution concentrated to afford 704 mg of [2R-hydroxy-3-[(4-methoxyphenyl)sulfonyl] (2-methylpropyl)amino]-1S-
10 (phenylmethyl)propylamine, mass spectrum m/e = 407 (M+H), which was used directly in the next step without purifi-
cation.

Part D:

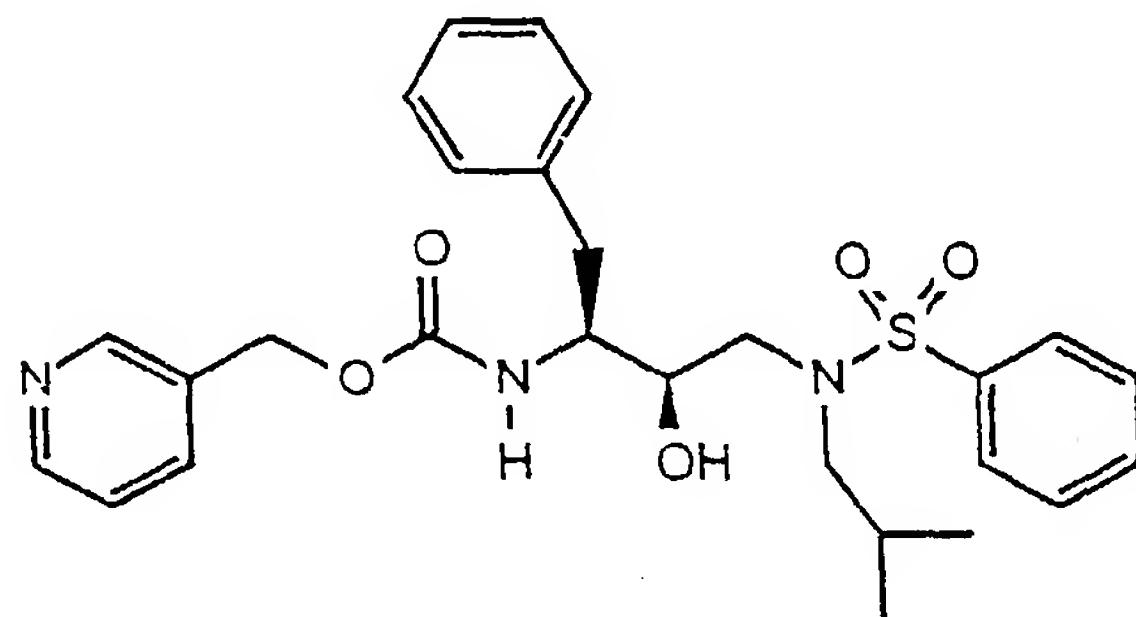
15 To a solution of 2.5g (22.9 mmol) of 3-pyridylcarbinol in 100 mL of anhydrous acetonitrile was added 8.8 g (34.4
mmol) of N,N'-disuccinimidyl carbonate and 5.55 mL (68.7 mmol) of pyridine. The solution was stirred for 1 hour and
then concentrated in vacuo. The residue was dissolved in ethyl acetate, then washed with saturated sodium bicarbo-
nate, brine, dried over magnesium sulfate, filtered and concentrated to afford 5.3 g of N-Hydroxysuccinimide-3-pyri-
dylmethyl carbonate, mass spectrum m/e = 251 (M+H), which was used directly in the next step without purification.

Part E:

20 To a solution of the amine from part C (2.87g, 7.0 mmol) and 1.38 mL of triethylamine in 24 mL of anhydrous
methylene chloride was added a solution of 1.65g (6.6 mmol) of N-hydroxysuccinimide-3-pyridyl carbonate from part D
25 in 24 mL of methylene chloride. The solution was stirred for 1 hour, 100 mL of methylene chloride added, then washed
with saturated sodium bicarbonate, brine, dried over sodium sulfate, filtered and concentrated to afford 3.69 g of crude
product. Chromatography on silica gel using 2% methanol/methylene chloride to afford 3.27 g of carbamic acid, [2R-
hydroxy-3-[(4-methoxyphenyl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propyl]-, 3-pyridylmethyl ester,
mass spectrum m/e = 548 (M+Li).

Example 13C

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45 Preparation of Carbamic acid, [2R-hydroxy-3-[(phenylsulfonyl)(2-methylpropyl)amino]-1S-(phenylmethyl)propyl]-,
3-pyridylmethyl ester

Part A:

50 A solution of N-benzyloxycarbonyl-3S-amino-1,2-S-epoxy-4-phenylbutane (50g, 0.168 mol) and isobutylamine
(246g, 3.24 mol) in 650 mL of isopropyl alcohol was refluxed for 1.25 hours. The solution was cooled to room temper-
ature, concentrated in vacuo and then poured into 1L of stirring hexane whereupon the product crystallized from so-
lution, was collected and air dried to give 57.6 g of N-[3S-benzyloxycarbonylamino-2R-hydroxy-4-phenyl]-N-isob-
utylamine, mp 108-109.5 C, mass spectrum m/e=371(M+H).

55 Part B:

The amine from part A (0.94g, 2.5 mmol) and triethylamine (288 mg, 2.85 mmol) in 20 mL of methylene chloride
was treated with 461 mg (2.61 mmol) of benzenesulfonyl chloride. The solution was stirred at room temperature for 16

hours, concentrated, dissolved in ethyl acetate, then washed with 1N potassium hydrogen sulfate, saturated sodium bicarbonate, brine, dried over magnesium sulfate, filtered and concentrated to afford a clear oil. This was recrystallized from diethyl ether and hexane to afford 0.73 g of carbamic acid, [2R-hydroxy-3-[(phenylsulfonyl)(2-methylpropyl)amino]-1S-(phenylmethyl)propyl]-, phenylmethyl ester, mp 95-99 C, mass spectrum m/e=511 (M+H).

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Part C:

A solution of 500mg of carbamic acid, [2R-hydroxy-3-[(phenylsulfonyl)(2-methylpropyl)amino]-1S-(phenylethyl)propyl]-, phenylmethyl ester in 20 mL of methanol was hydrogenated in the presence of 250 mg of a 10% palladium on carbon catalyst under 40 psig for 3 hours, the catalyst was removed by filtration, and the solution concentrated to afford 352 mg of [2R-hydroxy-3-[(phenylsulfonyl)]2-methylpropyl)amino]-1S-(phenylmethyl)propylamine, mass spectrum m/e = 377 (M+H), which was used directly in the next step without purification.

Part D:

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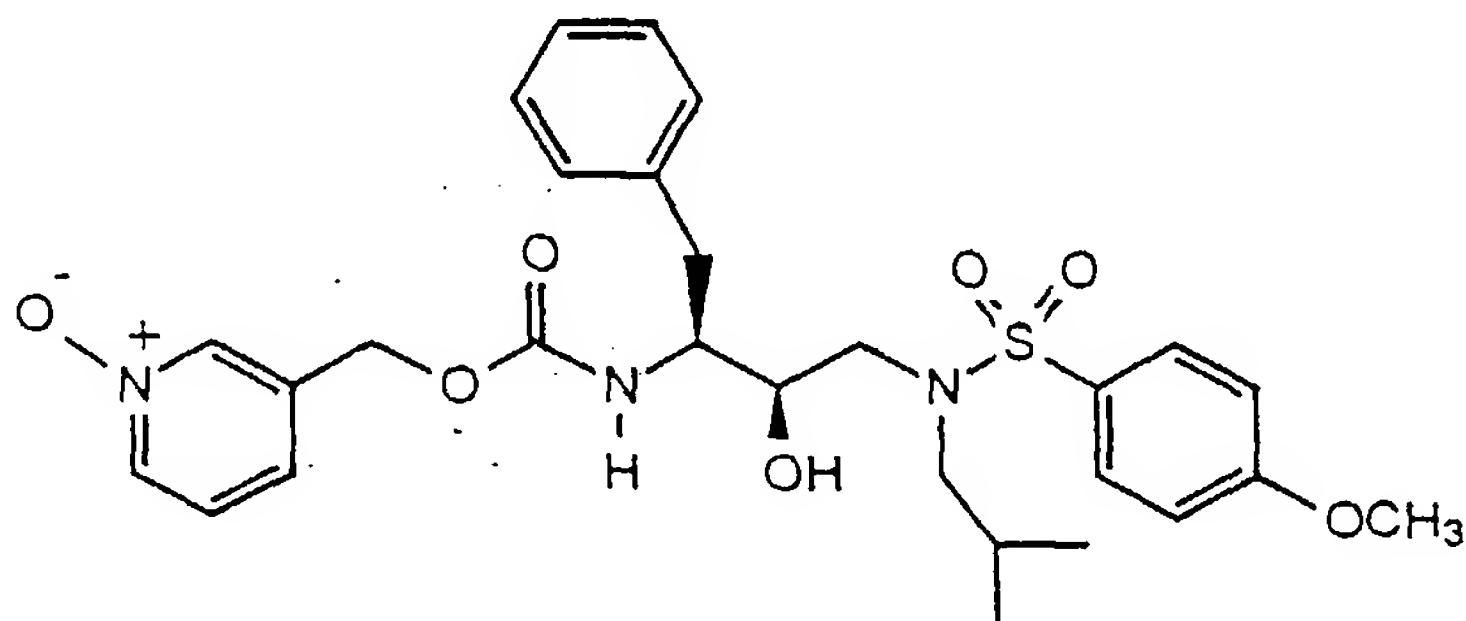
To a solution of 1.24 mmol of 5-norbornene-2,3-dicarboximido carbonochloridate (Henklein, P., et. al., Synthesis 1987, 166-167) in 1 mL of anhydrous methylene chloride, was added a solution of 43 µL (2.44 mmol) of 3-pyridylcarbinol and 129 µL (1.6 mmol) of pyridine in 1 mL of methylene chloride at 0°C under a nitrogen atmosphere. After 4 hours at room temperature, 150 mg (0.4 mmol) of [2R-hydroxy-3-[(phenylsulfonyl)]2-methylpropyl)amino]-1S(phenylmethyl)propylamine from Part C above was added and 100 µL of pyridine. After stirring for 15 hours at room temperature, ethyl acetate was added, then washed with 1N hydrochloric acid, saturated sodium bicarbonate, brine, dried over magnesium sulfate, filtered and concentrated to afford 175 mg of crude product. Chromatography over silica gel using 1% methanol/methylene chloride to afford 69 mg of pure carbamic acid, [2R-hydroxy-3-[(phenylsulfonyl)(2-methylpropyl)amino]-1S-(phenylmethyl)propyl]-, 3-pyridylmethyl ester, mass spectrum m/e = 512.2267 (M+H); calcd for C₂₇H₃₃N₃O₅S, 512.2219.

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Example 13D

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Preparation of Carbamic acid, [2R-hydroxy-3-[(4-methoxyphenyl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propyl]-, 3-pyridylmethyl ester, N-oxide

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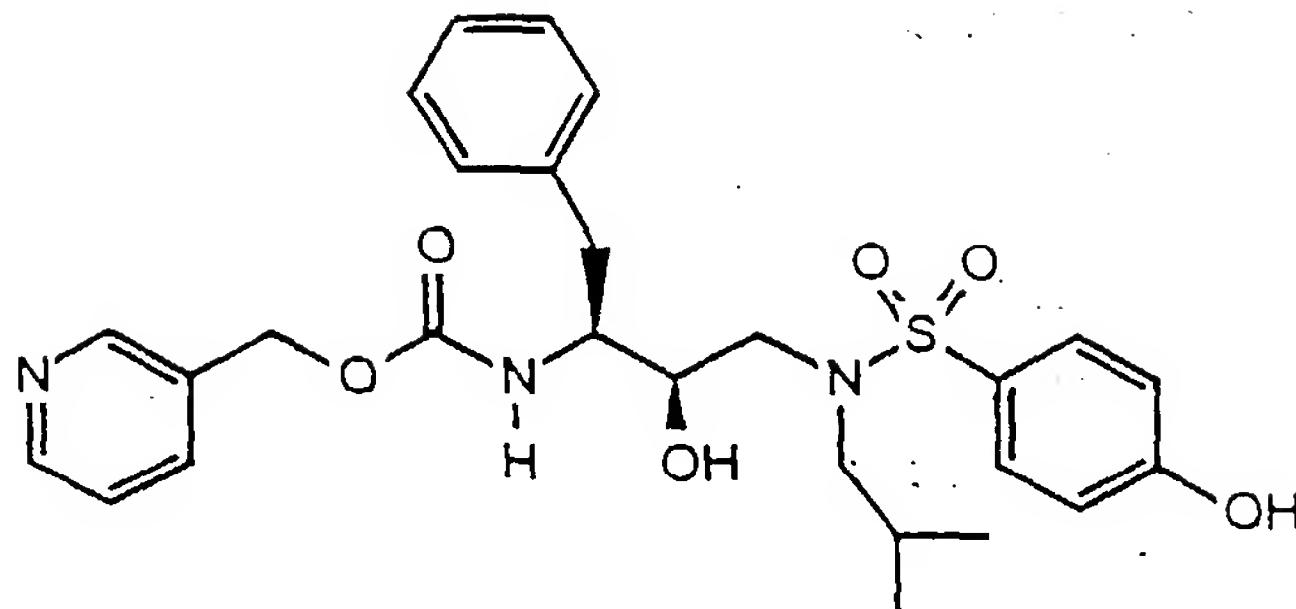
To a solution of 211mg (0.39 mmol) of carbamic acid, [2R-hydroxy-3-[(4-methoxyphenyl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propyl]-, 3-pyridylmethyl ester in 5mL of methylene chloride at 0 C was added 500 mg of 50% 3-chloroperbenzoic acid. After stirring at room temperature for 1 hour, ethyl acetate was added, the solution washed with saturated sodium bicarbonate, 0.2N ammonium hydroxide solution and brine, dried over magnesium sulfate, filtered and concentrated to afford 200 mg of crude product. This was chromatographed on C18 reverse phase material using 20-40% acetonitrile/water, then 100% acetonitrile to afford 90mg of the desired product, which was then recrystallized from ethyl acetate/isooctane to yield 34mg of pure carbamic acid, [2R-hydroxy-3-[(4-methoxyphenyl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propyl]-, 3-pyridylmethyl ester, N-oxide; mass spectrum m/e=564 (M+Li).

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Example 13E

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15 Preparation of Carbamic acid, [2R-hydroxy-3-[(4-hydroxyphenyl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propyl-, 3-pyridylmethyl ester

Part A:

20 A solution of 0.98 g (1.85 mmol) of carbamic acid, [2R-hydroxy-3-[(4-fluorophenyl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propyl-phenylmethyl ester in 3.8 mL of anhydrous DMF was added to 22mg (7.4 mmol) of 80% sodium hydride in 2 mL of DMF. To this mixture was added 0.40g (3.7 mmol) of benzyl alcohol. After 2 hours, the solution was cooled to 0 °C, water added, and then ethyl acetate. The organic layer was washed with 5% citric acid, saturated sodium bicarbonate and brine, dried over magnesium sulfate, filtered and concentrated to afford 0.90g of crude material. This was chromatographed on basic alumina using 3% methanol/methylene chloride to afford 0.70g of 2R-hydroxy-3-[(2-methylpropyl)(4-hydroxyphenyl)sulfonyl]amino-1S-(phenylmethyl)propylamine, cyclic carbamate; mass spectrum m/e=509 (M+H).

Part B:

30 To a solution of 0.65g (1.28 mmol) of the cyclic carbamate from part A in 15 mL of ethanol, was added 2.6 mL (6.4 mmol) of 2.5N sodium hydroxide solution. After 1 hour at reflux, 4 mL of water was added and the solution refluxed for an additional eight hours. The volatiles were removed, ethyl acetate added, and washed with water, brine, dried over magnesium sulfate, filtered and concentrated to afford 550 mg of crude 2R-hydroxy-3-[(2-methylpropyl) (4-hydroxy-phenyl)sulfonyl]amino-1S-(phenylmethyl)propylamine.

Part C:

40 A solution of crude 2R-hydroxy-3-[(2-methylpropyl) (4-benzyloxyphenyl)sulfonyl]amino-1S-(phenylmethyl)propylamine in 10 mL of ethanol was hydrogenated in the presence of 500 mg of a 10% palladium on carbon catalyst under 50 psig of hydrogen for 2 hours. The catalyst was removed by filtration and the solvent removed in vacuo to afford 330 mg of 2R-hydroxy-3-[(2-methylpropyl)(4-hydroxyphenyl)sulfonyl]amino-1S-(phenylmethyl)propylamine, mass spectrum m/e = 393 (M+H).

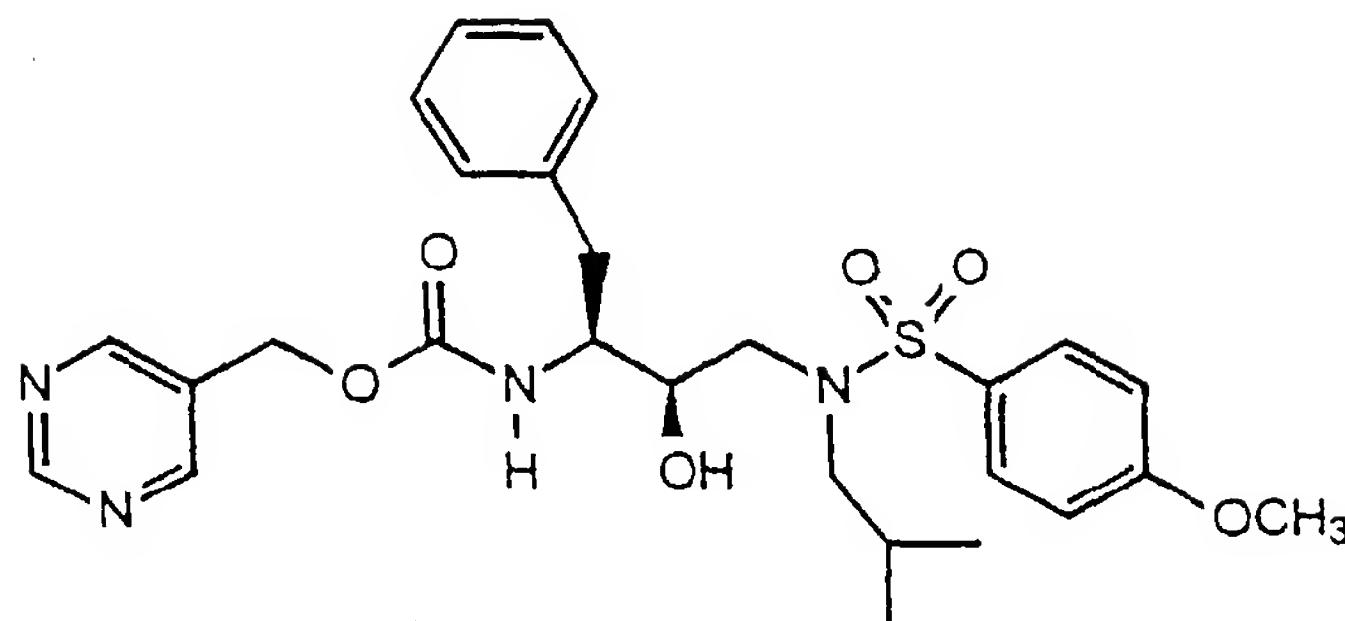
Part D:

45 To a solution of 320 mg (0.82 mmol) of the amine from part C in 6 mL of DMF, was added 192 mg (0.76 mmol) of N-hydroxysuccinimide-3-pyridylmethyl carbonate. After 15 hours at room temperature, the DMF was removed in vacuo, ethyl acetate added, washed with water, brine, dried with magnesium sulfate, filtered and concentrated to afford 390 mg of crude material. Chromatography on silica gel using 50-80% ethyl acetate/hexane afforded 180 mg of carbamic acid, [2R-hydroxy-3-[(4-hydroxyphenyl)sulfonyl](2-methylpropyl) amino] -is(phenylmethyl)propyl] -, 3-pyridylmethyl ester, mass spectrum m/e = 528(M+H).

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Example 13F

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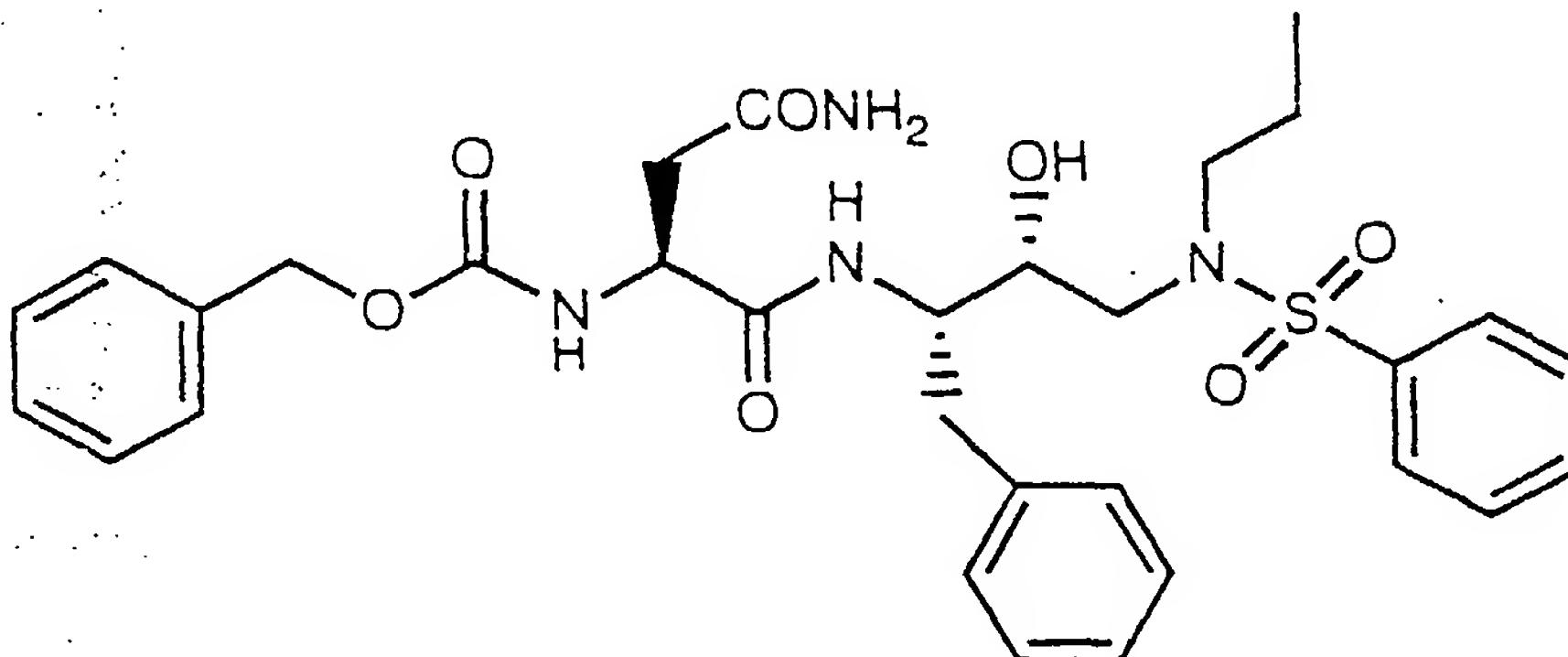
15

Preparation of Carbamic acid, [2R-hydroxy-3-[(4-methoxyphenyl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propyl-, 5-pyrimidylmethyl ester

To a solution of 9.5mg (0.09mmol) of 5-pyrimidylcarbinol in 1mL of anhydrous acetonitrile at room temperature, was added 24mg (0.09mmol) of N,N'-disuccinimidyl carbonate and 19.1 μ L (0.24mmol) of pyridine. After stirring for 5 hours , 32 mg (0.08mmol) of 2R-hydroxy-3-[(2-methylpropyl)(4-methoxyphenyl)sulfonyl]amino-1S-(phenylmethyl)propylamine was added and the solution stirred for 48 hours. After concentration in vacuo, methylene chloride was added, then washed with a 1:1 mixture of saturated sodium bicarbonate and brine, dried over magnesium sulfate, filtered and concentrated to give 27 mg of crude product. Chromatography on silica gel using 2% methanol/methylene chloride afforded 22 mg of the desired product, mass spectrum m/e=543 (M+H).

Example 14

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Preparation of phenylmethyl[3-amino-1S-[2R-hydroxy-3-[(3-propyl)(phenylsulfonyl)amino]-1S-(phenylmethyl)amino]-carbonyl]-3-oxopropyl]carbamate

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Phenylmethyl[2R-hydroxy-3-[(3-propyl)(phenylsulfonyl)amino]-1S-(phenylmethyl)propyl]-carbamate (200 mg, 0.40 mmol) was deprotected by hydrogenation over 10% palladium on carbon and the resulting free amine was coupled with N-CBZ-L-asparagine (157 mg, 0.42 mmol) in the presence of N-hydroxybenzotriazole (114 mg, 0.84 mmol) and EDC (130 mg, 0.67 mmol) to give phenylmethyl[3-amino-1S-[2R-hydroxy-3-[(3-propyl)(phenylsulfonyl)amino]-1S-(phenylmethyl)amino]carbonyl]-3-oxopropyl]carbamate as a solid. Anal. Calcd for C₃₁H₃₈N₄O₇S·0.2H₂O: C,60.61; H, 6.30; N,9.12. Found: C,60.27; H,6.16; N,8.93.

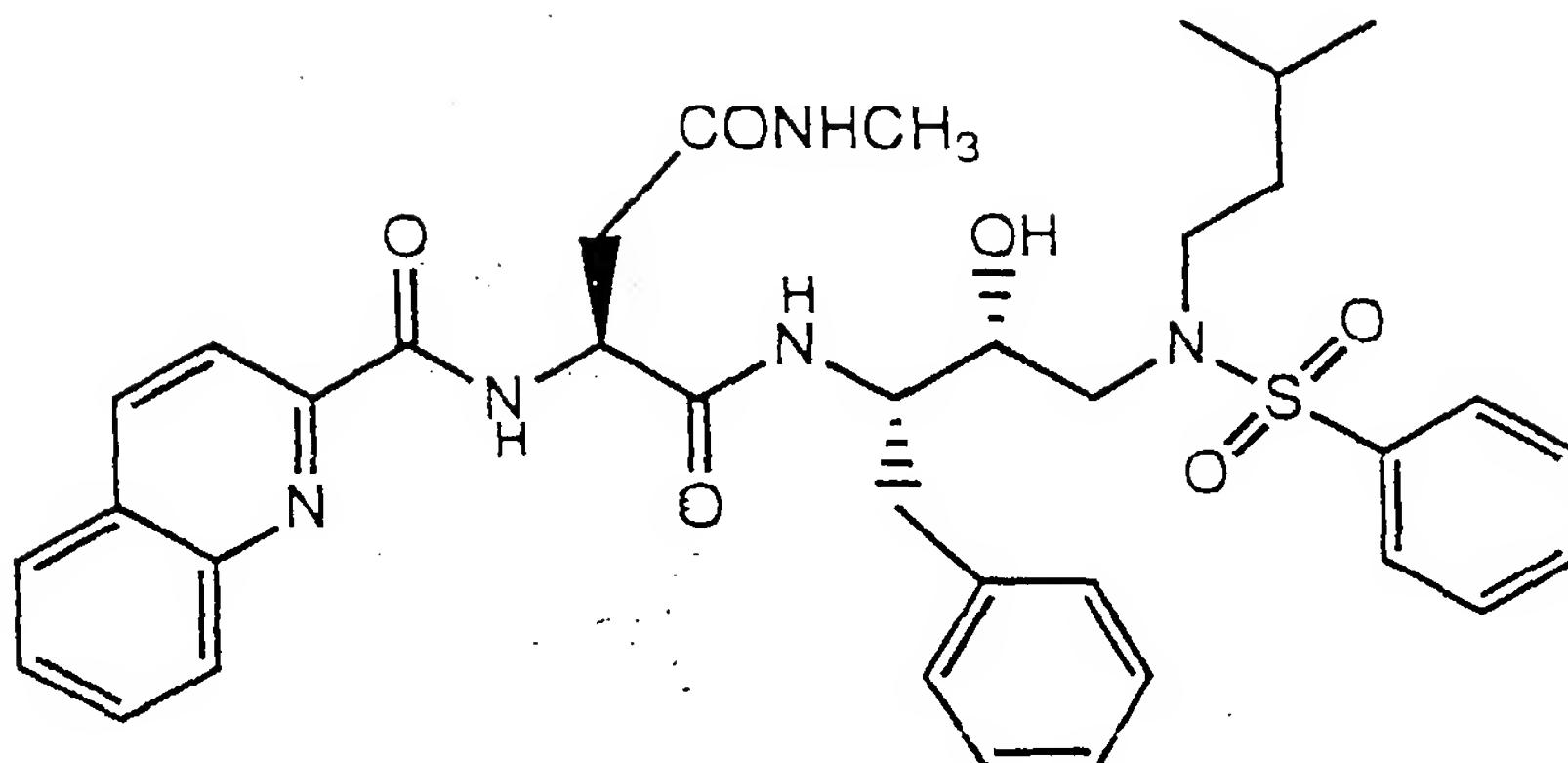
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Example 15A

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Preparation of N1-[2R-hydroxy-3-[(3-methylbutyl)(phenylsulfonyl)amino]-N4-methyl-1S-(phenylmethyl)propyl]-2S-[(2-quinolinylcarbonyl)amino]butanediamide

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Part A:

N2-[(1,1-dimethylethoxy)carbonyl]-N-methyl-L-asparagine was prepared from Boc-L-aspartic acid alphabenzyl ester(1.0 g, 3.09mmol), methylamine.HCl (209 mg, 3.09mmol), EDC(711 mg, 3.7 mmol), 1-hydroxybenzotriazole (627 mg, 4.63 mmol), and N-methylmorpholine (0.7 mL, 6.3 mmol), in DMF (20mL). After stirring overnight at r.t., the reaction mixture was diluted with ethyl acetate, washed with water, sat. sodium bicarbonate, 5% citric acid, brine, dried over magnesium sulfate and concentrated to an oil. The oil was taken up in 20 mL dry ethanol, and hydrogenated in the presence of 10% w/w of 10% Pd on C at atmospheric pressure and room temperature overnight. The mixture was filtered through Celite and concentrated to a white solid foam, 670 mg.

Part B:

A solution of phenylmethyl [2R-hydroxy-3-[(3-methylbutyl) (phenylsulfonyl)amino]-1S-(phenylmethyl)propyl]carbamate (310 mg, 0.59 mmol) in methanol (10mL) was hydrogenated over 10% palladium on carbon for 3 h., filtered through diatomaceous earth and concentrated to give the product as an oil (214 mg). This free amine (208 mg, 0.53 mmol) was coupled with N2-[(1,1-dimethylethoxy)-carbonyl]-N-methyl-L-asparagine (137 mg, 0.56 mmol) in the presence of N-hydroxybenzotriazole (102 mg, 0.76mmol) and EDC (130 mg, 0.67mmol) to yield 290 mg of N1[2R-hydroxy-3-[(3-methylbutyl)(phenylsulfonyl)amino]-N4-methyl-1S-(phenylmethyl)propyl]-2S-[(1,1-dimethylethoxy-carbonyl) amino]butane diamide.

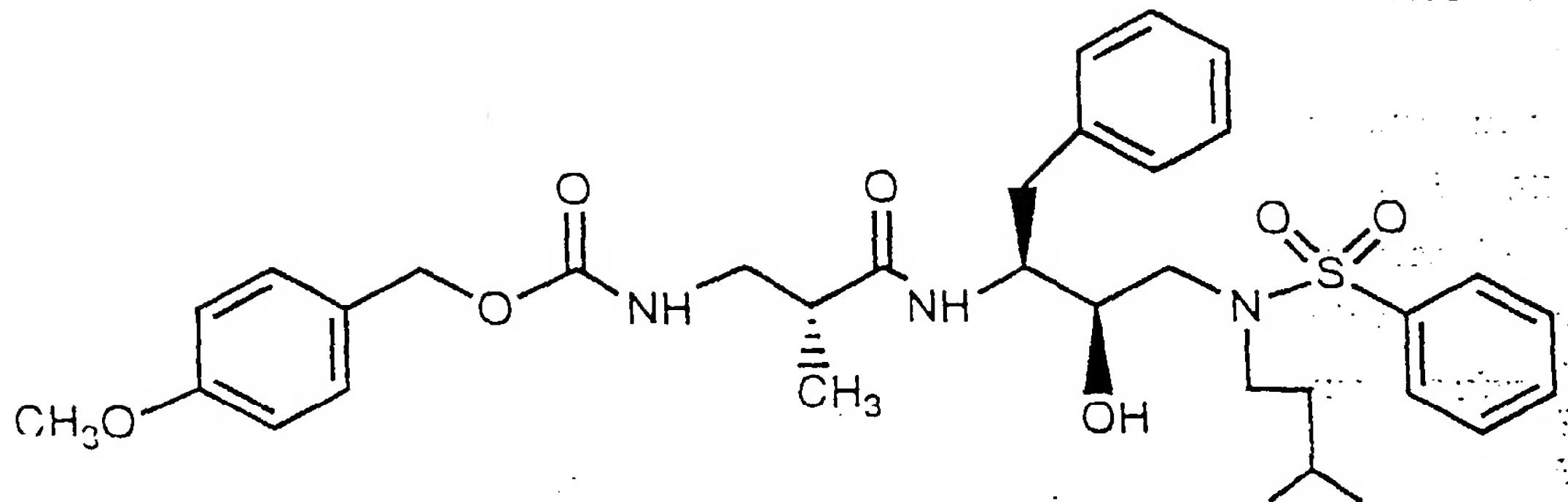
Part C:

N1[2R-hydroxy-3-[(3-methylbutyl) (phenylsulfonyl)amino]-N4-methyl-1S-(phenylmethyl)propyl]-2S-[(1,1-dimethyl-ethoxycarbonyl)-amino]butane diamide(270 mg, 0.43 mmol) was stirred in 4N HCl in dioxane (5 mL) at r.t. for 0.5 h. Solvent and excess reagent were evaporated to dryness. The product was dried in vacuo. This material (125 mg, 0.225 mmol) was then reacted with 2-quinoline carboxylic acid N-hydroxysuccimide ester (61 mg, 0.225 mmol), N-methyl-morpholine (50 uL, 0.45 mmol) in methylene chloride (2 mL) for 3 h. The product N1[2R-hydroxy-3-[(3-methylbutyl) (phenylsulfonyl)amino]-N4-methyl-1S-(phenylmethyl)propyl]-2S-[(2-quinolinylcarbonyl)-amino]butane diamide was purified by silica gel chromatography. Anal. Calcd for C₃₆H₄₃N₅O₆S·0.2H₂O: C,63.83; H,6.45; N,10.34. Found: C,63.64; H,6.40; N,10.34.

Example 15B

55

Following the procedures set forth above, the following compound was also prepared:



Thus, 4.10g, (7.8 mmol), of Carbamic acid, [2R-hydroxy-3-(3-methylbutyl)(phenylsulphonyl)amino]-1S-(phenylmethyl)propyl]-, phenylmethyl ester, [R-(R*,S*)]- was hydrogenated in a solution of methanol and ethanol using catalytic Pd/C 10% at 50 psig hydrogen for 3 hours. The catalyst was filtered and the solvents removed in vacuo to yield 3.0 grams of free amine.

In a separate flask, 2.09g, (7.8 mmol), of N-Moz-AMBA was added to 10 mL of dimethylformamide and 1.58g, (1.5 equiv.), of N-hydroxybenzotriazole and the solution was cooled to 5 degrees C. To this solution was added 1.49g, (7.8 mmol), of EDC and the solution stirred for 30 min. To this was added the free amine in 10 mL of dimethylformamide, and the reaction was stirred for 20 hours. The solvent was removed by evaporation and the crude material was partitioned between ethyl acetate and saturated aqueous sodium bicarbonate. The ethyl acetate layer was washed with 5% potassium hydrogen sulfate and brine, dried over magnesium sulfate, filtered and concentrated to yield 2.58 grams of pure product after recrystallization from ethyl acetate, ether, and hexanes. 52% yield.

30 Example 16

Following the procedures of Examples 1-15, the compounds shown in Table 3 were prepared.

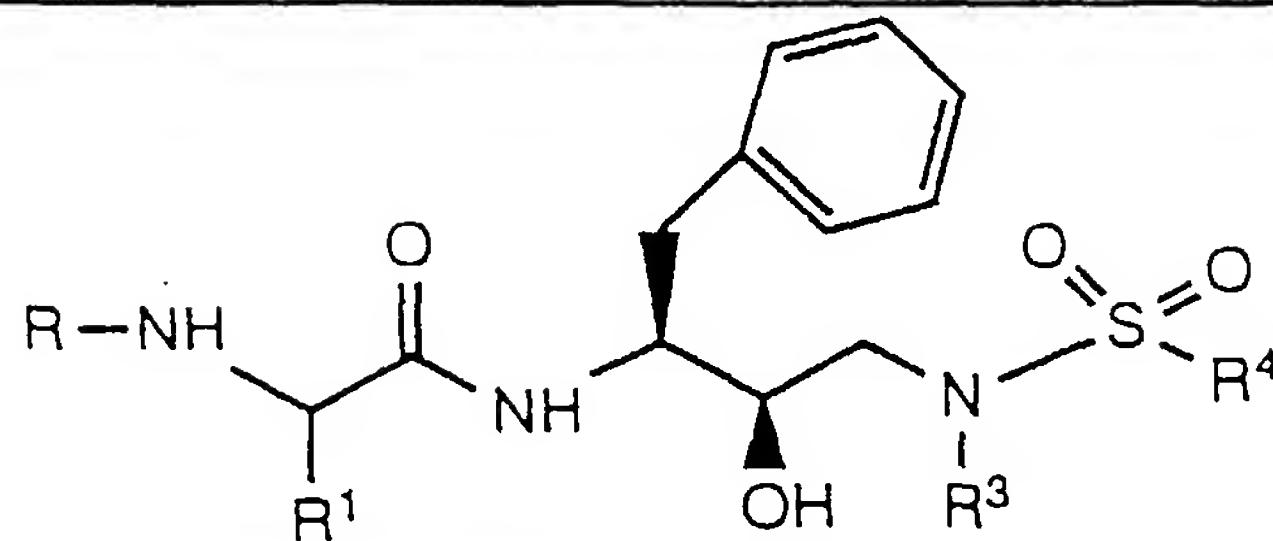
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TABLE 3

<u>Entry No.</u>	<u>R</u>	<u>R¹ R³</u>	<u>R⁴</u>
20 1	Cbz	t-Butyl	i-Amyl Methyl
2 2	N,N-Dimethylglycine	t-Butyl	i-Amyl Methyl
25 3	Cbz	i-Propyl	i-Amyl Phenyl
4 4	Cbz	sec-Butyl	i-Amyl Phenyl
5 5	Cbz	CH ₂ C(O)NH ₂	n-Propyl Phenyl
6 6	N-Methylglycine	t-Butyl	i-Amyl Phenyl
7 7	Cbz	t-Butyl	i-Butyl Phenyl
30 8	N,N-Dimethylglycine	t-Butyl	i-Amyl Phenyl
9 9	N-Methylglycine	t-Butyl	i-Amyl Phenyl
10 10	N,N-Dimethylglycine	t-Butyl	i-Butyl (4-OCH ₃)Phenyl
35 11	N-Methylglycine	t-Butyl	i-Butyl (4-OCH ₃)Phenyl

40

45

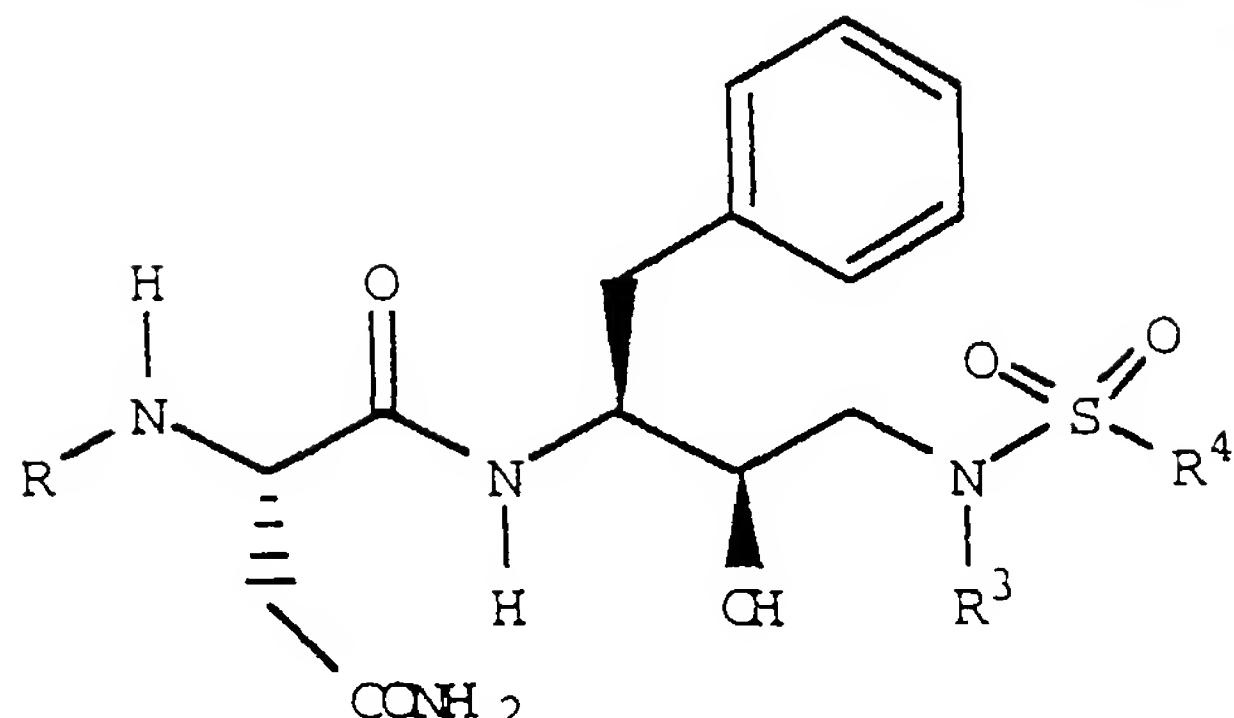
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TABLE 4

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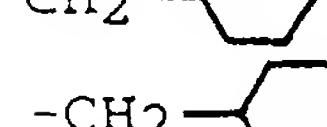
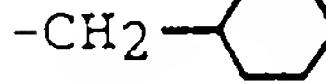
Entry No.	R	R ³	R ⁴
1	Cbz ^a	CH ₃	n-Butyl
2	Cbz	i-Butyl	CH ₃
3	Cbz	i-Butyl	n-Butyl
4	Q ^b	i-Butyl	n-Butyl
5	Cbz	i-Propyl	n-Butyl
6	Q	i-Propyl	n-Butyl
7	Cbz	C ₆ H ₅	n-Butyl
8	Cbz	-CH ₂ -C ₆ H ₅	n-Butyl
9	Cbz	-CH ₂ -C ₆ H ₄ -C ₆ H ₅	n-Butyl
10	Q	-CH ₂ -C ₆ H ₄ -C ₆ H ₅	n-Butyl
11	Cbz	-C ₆ H ₅	n-Butyl
12	Cbz	i-Butyl	n-Propyl

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TABLE 4 (Cont'd.)

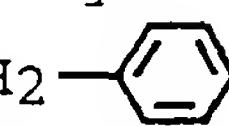
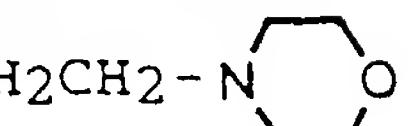
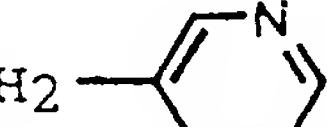
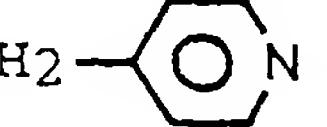
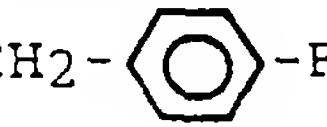
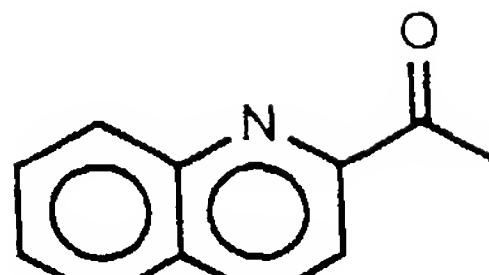
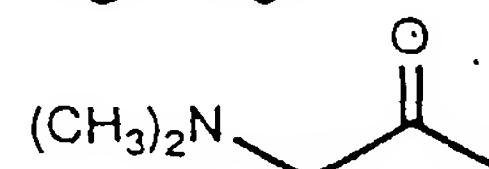
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	Entry No.	R	R ³	R ⁴
10	13	Cbz	i-Butyl	-CH ₂ CH(CH ₃) ₂
	14	Cbz	(R)-CH(CH ₃)- 	n-Butyl
15	15	Cbz	CH ₂ - 	i-Propyl
	16	Cbz	-CH ₂ - 	-CH ₂ CH ₂ CH(CH ₃) ₂
	17	Cbz	i-Butyl	-CH ₂ CH ₃
20	18	Cbz	i-Butyl	-CH(CH ₃) ₂
	19	Cbz	i-Butyl	 
25	20	Q	-Butyl	 
	21	Cbz	-CH ₂ - 	- (CH ₂) ₂ CH(CH ₃) ₂
	22	Cbz	(CH ₂) ₂ CH(CH ₃) ₂	-CH(CH ₃) ₂
30	23	Q	i-Butyl	-CH(CH ₃) ₂
	24	Cbz	i-Butyl	-C(CH ₃) ₃
	25	Q	i-Butyl	-C(CH ₃) ₃
35	26	Cbz	-CH ₂ - 	-C(CH ₃) ₃
	27	Q	-CH ₂ - 	-C(CH ₃) ₃
40	28	Cbz	- (CH ₂) ₂ CH(CH ₃) ₂	-C(CH ₃) ₃
	29	Q	- (CH ₂) ₂ CH(CH ₃) ₂	-C(CH ₃) ₃
	30	Cbz	-CH ₂ C ₆ H ₅	-C(CH ₃) ₃
45	31	Q	-CH ₂ C ₆ H ₅	-C(CH ₃) ₃
	32	Cbz	- (CH ₂) ₂ C ₆ H ₅	-C(CH ₃) ₃
50	33	Cbz	- (CH ₂) ₂ C ₆ H ₅	-C(CH ₃) ₃
	34	Cbz	n-Butyl	-C(CH ₃) ₃

55

TABLE 4 (Cont'd.)

5

Entry No.	R	R ³	R ⁴
35	Cbz	n-Pentyl	-C(CH ₃) ₃
36	Cbz	n-Hexyl	-C(CH ₃) ₃
37	Cbz	-CH ₂ - 	-C(CH ₃) ₃
38	Cbz	-CH ₂ C(CH ₃) ₃	-C(CH ₃) ₃
39	Q	-CH ₂ C(CH ₃) ₃	-C(CH ₃) ₃
40	Cbz	-CH ₂ CH ₂ - 	-C(CH ₃) ₃
41	Cbz	-CH ₂ C ₆ H ₅ OCH ₃ (para)	-C(CH ₃) ₃
42	Cbz	-CH ₂ - 	-C(CH ₃) ₃
43	Cbz	-CH ₂ - 	-C(CH ₃) ₃
44	Cbz	-(CH ₂) ₂ C(CH ₃) ₃	-C(CH ₃) ₃
45	Q	-(CH ₂) ₂ C(CH ₃) ₃	-C(CH ₃) ₃
46	Cbz	-(CH ₂) ₄ OH	-C(CH ₃) ₃
47	Q	-(CH ₂) ₄ OH	-C(CH ₃) ₃
48	Q	-CH ₂ - 	-C(CH ₃) ₃
49	Q	-CH ₂ - 	-C(CH ₃) ₃
50	Cbz	-CH ₂ CH(CH ₃) ₂	-C ₆ H ₅
51		-CH ₂ CH(CH ₃) ₂	-C ₆ H ₅
52		-CH ₂ CH(CH ₃) ₂	-C ₆ H ₅

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TABLE 4 (Cont'd.)

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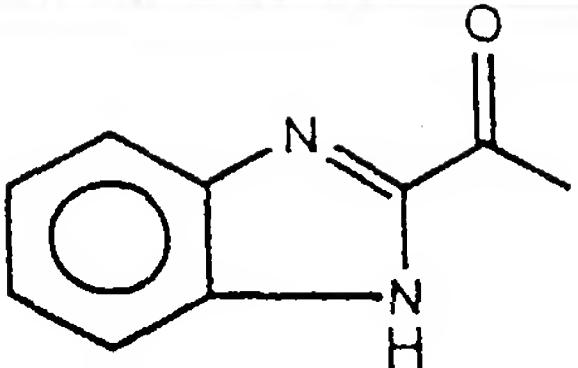
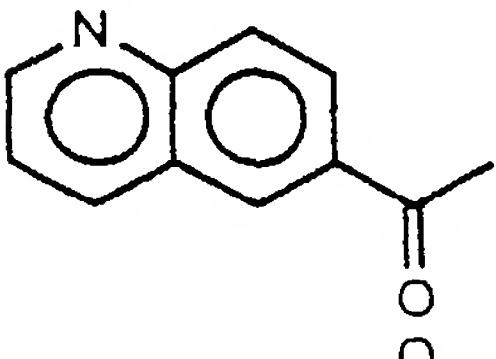
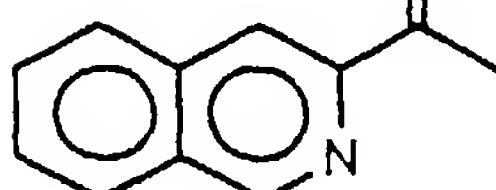
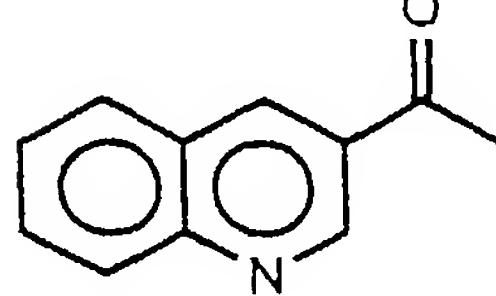
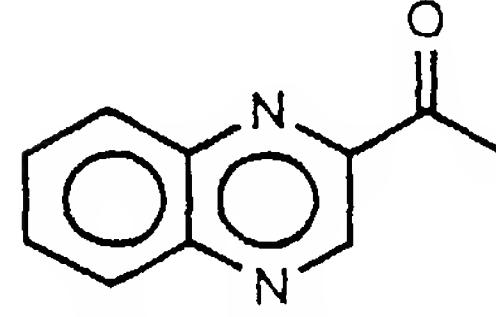
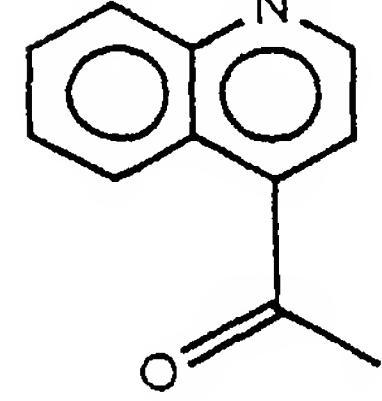
Entry No.	R	R ³	R ⁴
53		-CH ₂ CH(CH ₃) ₂	-C ₆ H ₅
54		-CH ₂ CH(CH ₃) ₂	-C ₆ H ₅
55		-CH ₂ CH(CH ₃) ₂	-C ₆ H ₅
56		-CH ₂ CH(CH ₃) ₂	-C ₆ H ₅
57		-CH ₂ CH(CH ₃) ₂	-C ₆ H ₅
58		-CH ₂ CH(CH ₃) ₂	-C ₆ H ₅
59		-CH ₂ CH(CH ₃) ₂	-C ₆ H ₅

50

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TABLE 4 (Cont'd.)

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Entry No.	R	R ³	R ⁴	
10				
15	60		-CH ₂ CH(CH ₃) ₂	-C ₆ H ₅
20	61		-CH ₂ CH(CH ₃) ₂	-C ₆ H ₅
25	62		-CH ₂ CH(CH ₃) ₂	-C ₆ H ₅
30	63		-CH ₂ CH(CH ₃) ₂	-C ₆ H ₅
35	64		-CH ₂ CH(CH ₃) ₂	-C ₆ H ₅
40	65		-CH ₂ CH(CH ₃) ₂	-C ₆ H ₅

50

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TABLE 4 (Cont'd.)

5

Entry No.	R	R ³	R ⁴
66		-CH ₂ CH(CH ₃) ₂	-C ₆ H ₅
67		-CH ₂ CH(CH ₃) ₂	-C ₆ H ₅
68		-CH ₂ CH(CH ₃) ₂	-C ₆ H ₅
69		-CH ₂ CH(CH ₃) ₂	-C ₆ H ₅
70	Q	-CH ₂ Ph	-Ph
71	Q	-CH ₂ --F	-Ph
72	Q	-CH ₂ -	-Ph
73	Q	-CH ₂ --OCH ₃	-Ph
74	Q	-CH ₂ -	-Ph

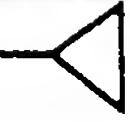
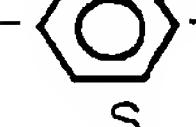
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TABLE 4 (Cont'd.)

5

	Entry No.	R	R ³	R ⁴
10	75	Q	-CH ₂ 	-Ph
15	76	Q	-CH ₂ CH=CH ₂	-Ph
20	77	Q	- 	-Ph
25	78	Q	- 	-Ph
30	79	Q	-CH ₂ CH ₂ Ph	-Ph
35	80	Q	-CH ₂ CH ₂ CH ₂ CH ₂ OH	-Ph
40	81	Q	-CH ₂ CH ₂ N(CH ₃) ₂	-Ph
45	82	Q	-CH ₂ CH ₂ -N 	-Ph
50	83	Q	-CH ₃	-Ph
	84	Q	-CH ₂ CH ₂ CH ₂ SCH ₃	-Ph
	85	Q	-CH ₂ CH ₂ CH ₂ S(O) ₂ CH ₃	-Ph
	86	Q	-CH ₂ CH ₂ CH ₂ CH(CH ₃) ₂	- 
	87	Q	-CH ₂ CH ₂ CH(CH ₃) ₂	-CH ₂ - 
	88	Q	-CH ₂ CH ₂ CH(CH ₃) ₂	-CH ₂ CH ₂ CH ₃
	89	Q	-CH ₂ CH ₂ CH ₂ CH(CH ₃) ₂	-CH ₃
	90	Q	-CH ₂ CH ₂ CH(CH ₃) ₂	-  -F
	91	Q	-CH ₂ CH ₂ CH(CH ₃) ₂	- 
	92	Q	-CH ₂ CH ₂ CH(CH ₃) ₂	-  -NO ₂
	93	Q	-CH ₂ CH ₂ CH(CH ₃) ₂	- 

55

TABLE 4 (Cont'd.)

5

	Entry No.	R	R ³	R ⁴
10	94	Q	-CH ₂ CH ₂ CH(CH ₃) ₂	
15	95	Q	-CH ₂ CH ₂ CH(CH ₃) ₂	
20	96	Q	-CH ₂ CH ₂ CH(CH ₃) ₂	
25	97	Q	-CH ₂ CH ₂ CH(CH ₃) ₂	
30	98	Q	-CH ₂ CH ₂ CH(CH ₃) ₂	
35	99	Q	-CH ₂ CH ₂ CH(CH ₃) ₂	
40	100	Q	-CH ₂ CH ₂ CH(CH ₃) ₂	
45	101	Q	-CH ₂ CH ₂ CH(CH ₃) ₂	
	102	Q	-CH ₂ CH ₂ CH(CH ₃) ₂	
	103	Q	-CH ₂ CH(CH ₃) ₂	
	104	Q	-CH ₂ CH(CH ₃) ₂	
	105	Q	-CH ₂ CH(CH ₃) ₂	
	106	Q	-CH ₂ CH ₂ CH ₃	
	107	Q	-CH ₂ CH ₂ CH ₂ CH ₃	

a benzylloxycarbonyl

b 2-quinolinylcarbonyl

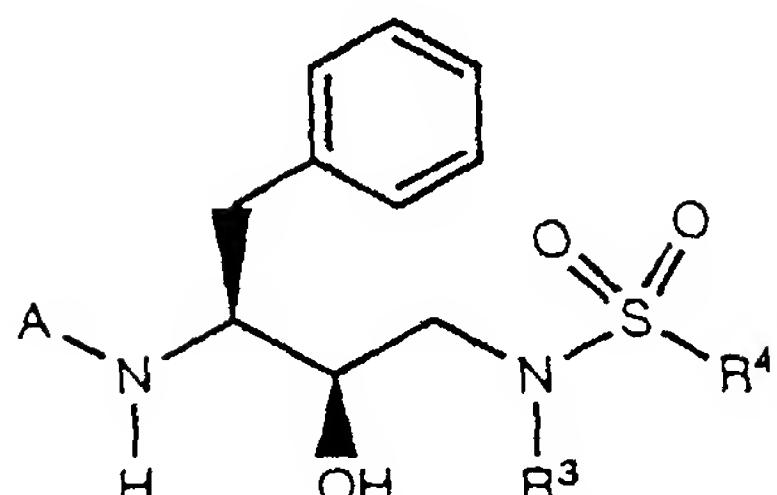
50

55

TABLE 5

5

10



15

Entry	A	R ³	R ⁴
1	Cbz-Val	i-amyl	-C ₆ H ₅
2	Cbz-Leu	i-amyl	-C ₆ H ₅
3	Cbz-Ile	i-amyl	-C ₆ H ₅
4	Ac-D-homo-Phe	i-Bu	methyl
5	Qui-Orn(g-Cbz)	-CH ₂ -	-C ₆ H ₅
6	Cbz-Asn	-CH ₂ CH=CH ₂	-C ₆ H ₅
7	Acetyl-t-BuGly	i-amyl	-C ₆ H ₅
8	Acetyl-Phe	i-amyl	-C ₆ H ₅
9	Acetyl-Ile	i-amyl	-C ₆ H ₅
10	Acetyl-Leu	i-amyl	-C ₆ H ₅
11	Acetyl-His	i-amyl	-C ₆ H ₅
12	Acetyl-Thr	i-amyl	-C ₆ H ₅
13	Acetyl-NHCH(C(CH ₃) ₂ (SCH ₃))C(O)-	i-amyl	-C ₆ H ₅
14	Cbz-Asn	i-amyl	-C ₆ H ₅
15	Cbz-Ala	i-amyl	-C ₆ H ₅
16	(N,N-dimethylglycinyl)Val	i-amyl	-C ₆ H ₅
17	(N-methylglycinyl)Val	i-amyl	-C ₆ H ₅
18	(N,N-dimethylglycinyl)Ile	i-amyl	-C ₆ H ₅
19	(N-methylglycinyl)Ile	i-amyl	-C ₆ H ₅

55

TABLE 5 (Cont'd)

5

Entry	A	R ³	R ⁴
10	20 Cbz-Ala	i-amyl	-C ₆ H ₅
	21 Cbz-beta-cyanoAla	i-amyl	-C ₆ H ₅
	22 Cbz-t-BuGly	i-amyl	-C ₆ H ₅
15	23 Q-t-BuGly	i-amyl	-C ₆ H ₅
	24 Q-SCH ₃ Cys	i-amyl	-C ₆ H ₅
	25 Cbz-SCH ₃ Cys	i-amyl	-C ₆ H ₅
20	26 Q-Asp	i-amyl	-C ₆ H ₅
	27 Cbz-(NHCH(C(CH ₃) ₂ (SCH ₃))C(O)-	i-amyl	-C ₆ H ₅
	28 Cbz-EtGly	i-amyl	-C ₆ H ₅
25	29 Cbz-PrGly	i-amyl	-C ₆ H ₅
	30 Cbz-Thr	i-amyl	-C ₆ H ₅
	31 Q-Phe	i-amyl	-C ₆ H ₅
	32 Cbz-Phe	i-amyl	-C ₆ H ₅
30	33 CH ₂ =CHCH ₂ O)C=O)	i-Butyl (4-OCH ₃)	-C ₆ H ₅ (4-OCH ₃)

35

40

45

50

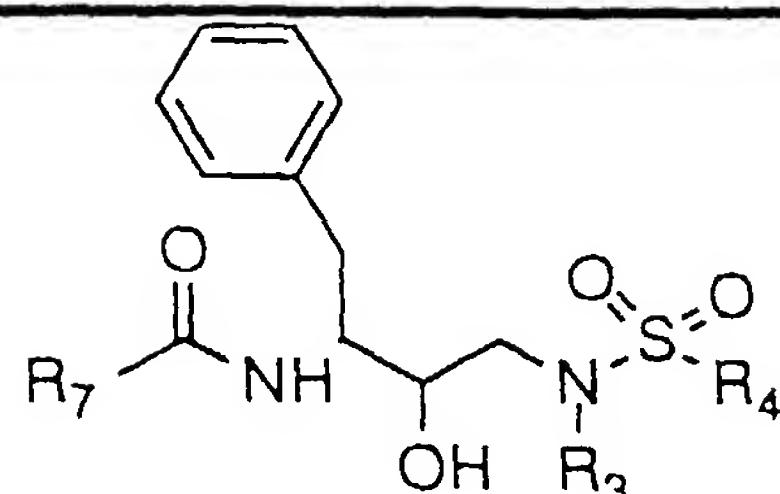
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TABLE 5A

5

Entry

10



15

MASS MEASUREMENT

20

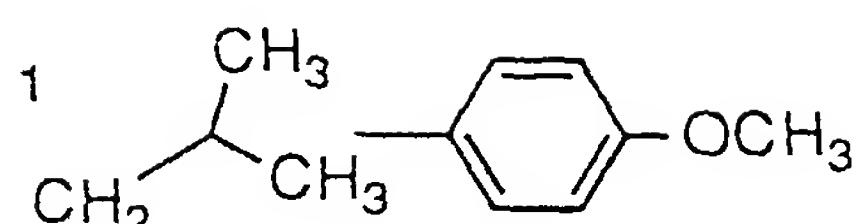
 R^3 R^4 R^7

MOL FORM

CALC
 $\text{M}+\text{H}$

FOUND

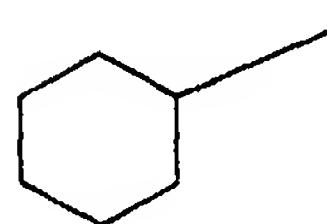
25

 $\text{C}_{27}\text{H}_{38}\text{N}_2\text{O}_5\text{S}$

503.2661 503.2624

30

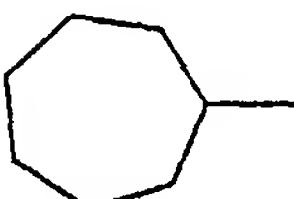
2

 $\text{C}_{28}\text{H}_{40}\text{N}_2\text{O}_5\text{S}$

517.2736 517.2777

35

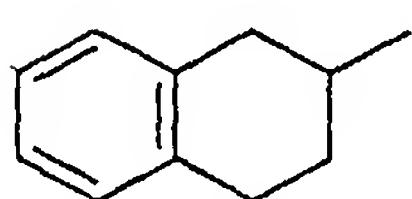
3

 $\text{C}_{29}\text{H}_{42}\text{N}_2\text{O}_5\text{S}$

531.2893 531.2916

40

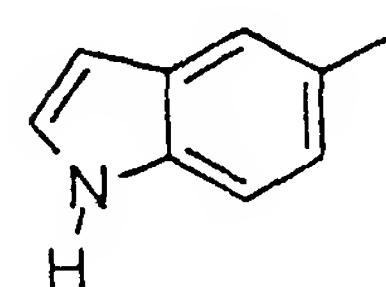
4

 $\text{C}_{32}\text{H}_{40}\text{N}_2\text{O}_5\text{S}$

565.2736 565.2731

45

5

 $\text{C}_{30}\text{H}_{35}\text{N}_3\text{O}_5\text{S}$

550.2376 550.2427

50

55

TABLE 5A (Cont'd)

5 Entry

				MASS MEASUREMENT		
	R ³	R ⁴	R ⁷	MOL FORM	CALC	FOUND
20				C ₃₀ H ₃₈ N ₂ O ₅ S	539(M+H)	539
25	7			C ₂₉ H ₃₆ N ₂ O ₅ S	?	?
30	8			C ₃₀ H ₃₈ N ₂ O ₅ S	539.2580 (M+H)	539.2591

35

40

45

50

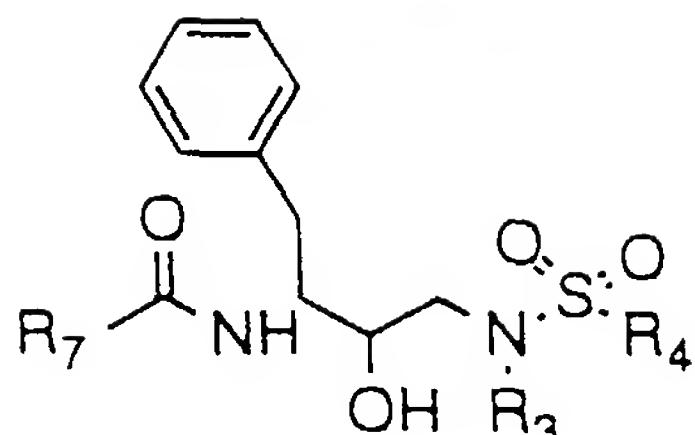
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TABLE 5A (Cont'd)

5

Entry

10



MASS MEASUREMENT

20

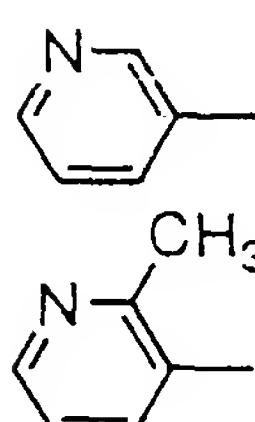
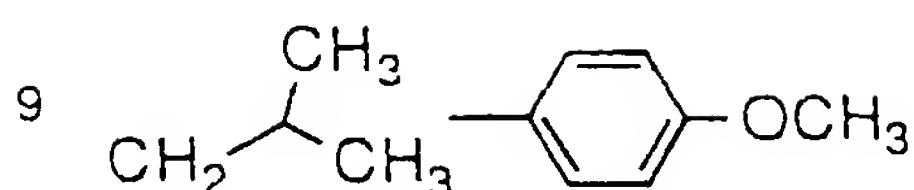
 R^3 R^4 R^7

MOL FORM

CALC
($M+H$)

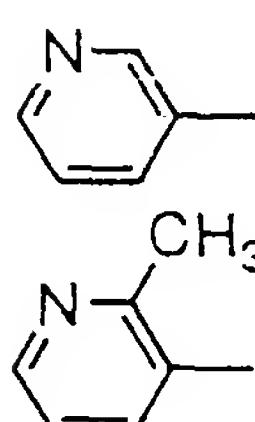
FOUND

15

 $C_{27}H_{33}N_3O_5S$ 512.2219

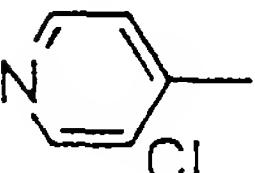
512.2271

25

 $C_{28}H_{35}N_3O_5S$ 526.2376

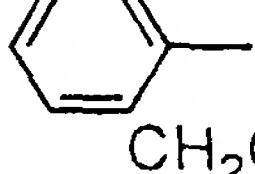
526.2388

30

 $C_{27}H_{33}N_3O_5S$ 512.2219

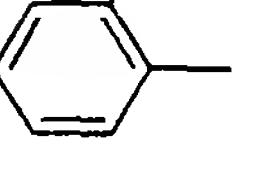
512.2287

35

 $C_{28}H_{33}N_2O_5ClS$ 545.1877

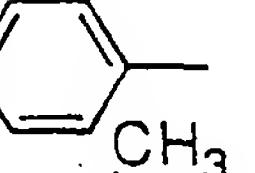
545.1887

40

 $C_{30}H_{38}N_2O_5S$ 539.2580

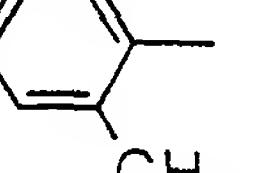
539.2592

45

 $C_{31}H_{40}N_2O_5S$ 553.2736

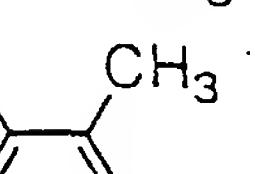
553.2714

50

 $C_{30}H_{38}N_2O_5S$ 539.2580

539.2632

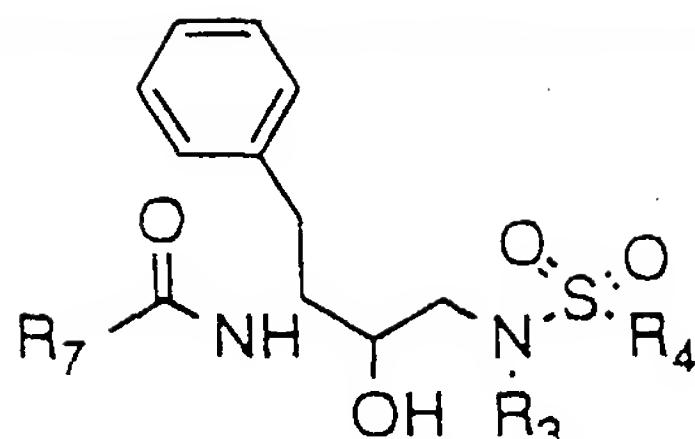
55

 $C_{30}H_{38}N_2O_5S$ 539 ($M+H$)

539

TABLE 5A (Cont'd)

5 Entry



MASS MEASUREMENT

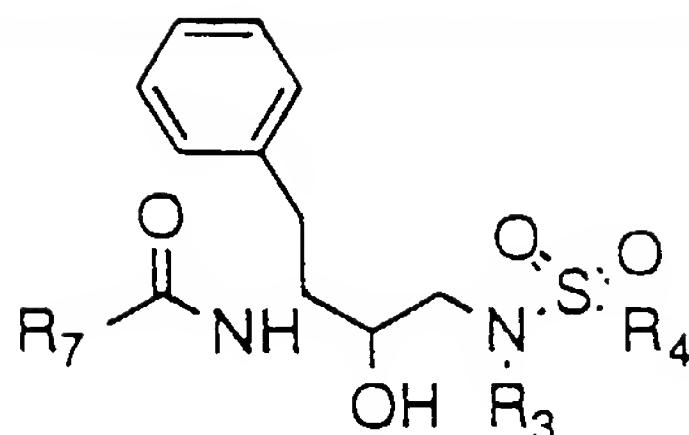
	R ³	R ⁴	R ⁷	MOL FORM	CALC	FOUND
20						
25	$^{17}\text{CH}_2\text{--}(\text{CH}_3)_2$	$\text{C}_6\text{H}_4\text{--OCH}_3$	$\text{C}_6\text{H}_4\text{--SO}_2\text{CH}_3$	$\text{C}_{29}\text{H}_{36}\text{N}_2\text{O}_7\text{S}_2$	589.2042 (M+H)	589.2086
30	18		$\text{C}_6\text{H}_4\text{--SO}_2\text{CH}_3$	$\text{C}_{29}\text{H}_{36}\text{N}_2\text{O}_7\text{S}_2$	595.2124 (M+Li)	595.2103
35	19		$\text{C}_6\text{H}_4\text{--SO}_2\text{CH}_2\text{CH}_3$	$\text{C}_{29}\text{H}_{36}\text{N}_2\text{O}_7\text{S}_2$	595.2124 (M+Li)	595.2191
40	20		$\text{C}_6\text{H}_4\text{--SO}_2\text{CH}_2\text{CH}_2\text{CH}_3$	$\text{C}_{30}\text{H}_{38}\text{N}_2\text{O}_7\text{S}_2$	609.2281 (M+Li)	609.2313
45	21		$\text{C}_6\text{H}_4\text{--SO}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$	$\text{C}_{30}\text{H}_{38}\text{N}_2\text{O}_7\text{S}_2$	603.2199 (M+H)	603.2247
50	22		$\text{C}_6\text{H}_4\text{--SO}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$	$\text{C}_{30}\text{H}_{38}\text{N}_2\text{O}_7\text{S}_2$	603.2199 (M+H)	603.2266

TABLE 5A (Cont'd)

5

Entry

10



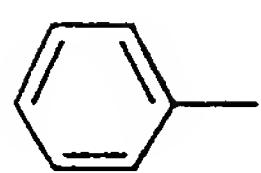
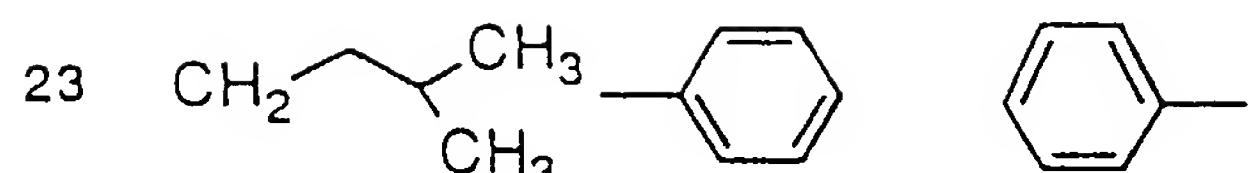
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EXACT MASS MEASUREMENT

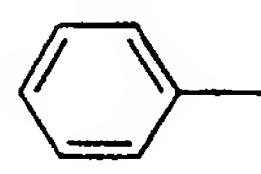
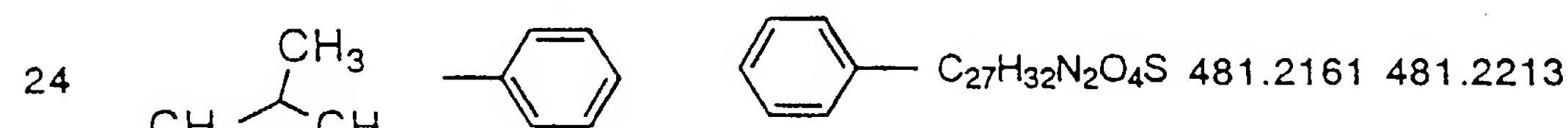
20

	R^3	R^4	R^7	MOL FORM	CALC ($\text{M}+\text{H}$)	FOUND
--	--------------	--------------	--------------	----------	---------------------------------	-------

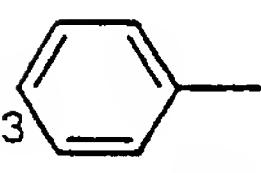
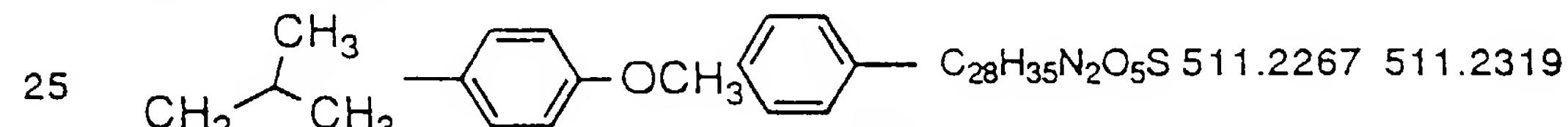
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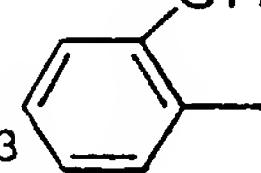
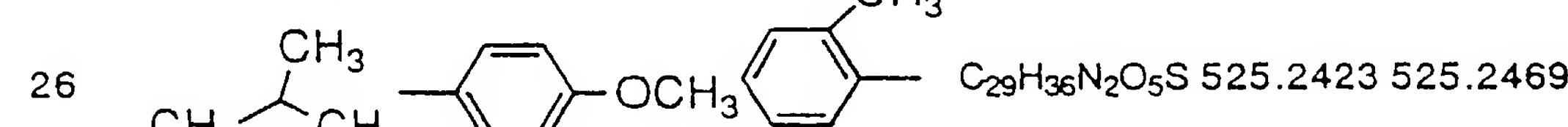
30

 $\text{C}_{27}\text{H}_{32}\text{N}_2\text{O}_4\text{S}$ 481.2161 481.2213

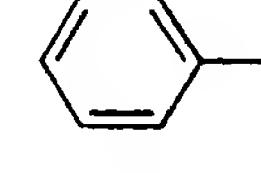
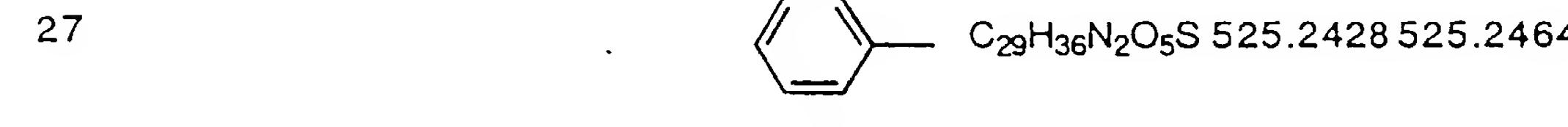
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 $\text{C}_{28}\text{H}_{35}\text{N}_2\text{O}_5\text{S}$ 511.2267 511.2319

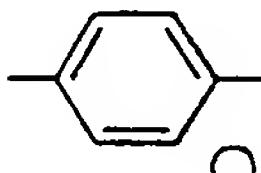
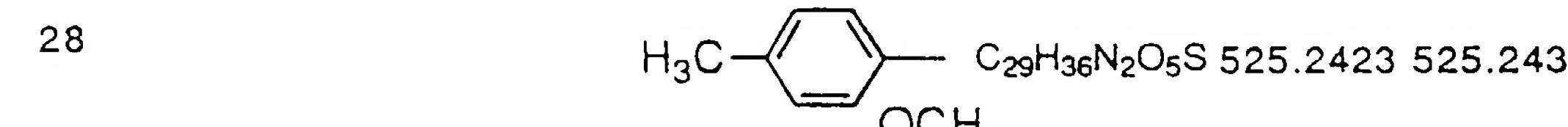
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 $\text{C}_{29}\text{H}_{36}\text{N}_2\text{O}_5\text{S}$ 525.2423 525.2469

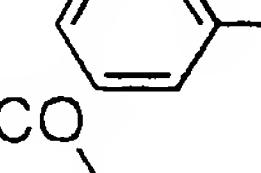
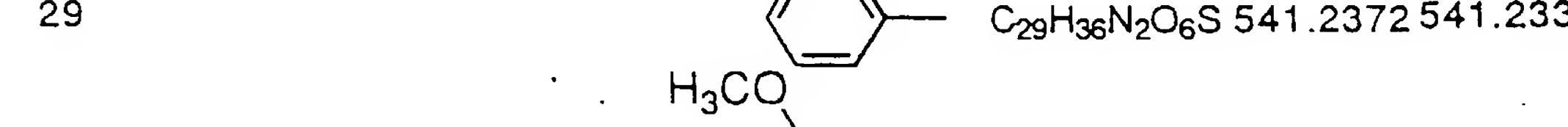
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 $\text{C}_{29}\text{H}_{36}\text{N}_2\text{O}_5\text{S}$ 525.2428 525.2464

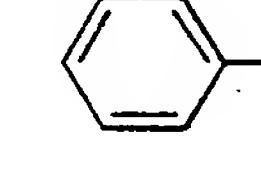
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 $\text{C}_{29}\text{H}_{36}\text{N}_2\text{O}_5\text{S}$ 525.2423 525.2432

55

 $\text{C}_{29}\text{H}_{36}\text{N}_2\text{O}_6\text{S}$ 541.2372 541.2332

56

 $\text{C}_{29}\text{H}_{36}\text{N}_2\text{O}_6\text{S}$ 541.2372 541.2355

57

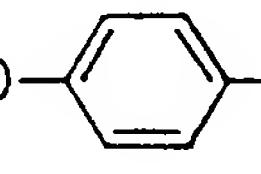
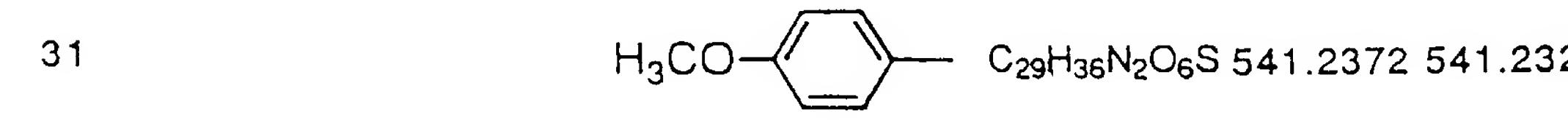
 $\text{C}_{29}\text{H}_{36}\text{N}_2\text{O}_6\text{S}$ 541.2372 541.2329

TABLE 5B

Table	Entry	IC ₅₀ (μM) or % inhibition
5	1A	0.02
	5A	0.04
	5A	0.02
	5A	0.01
10	5A	0.026
	5A	0.023
	5A	0.007
	5A	0.067
	5A	0.018
15	5A	0.006
	5A	0.0098
	5A	0.049
	5A	0.008
20	5A	59% @ 10μM
	5A	0.13
	5A	0.092
	5A	85% @ 1μM
25	5A	63% @ 1μM
	5A	0.047
	5A	0.014
	5A	0.005
	5A	0.015
30	5A	0.19
	5A	0.03
	5A	0.02

35

40

45

50

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TABLE 6

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30

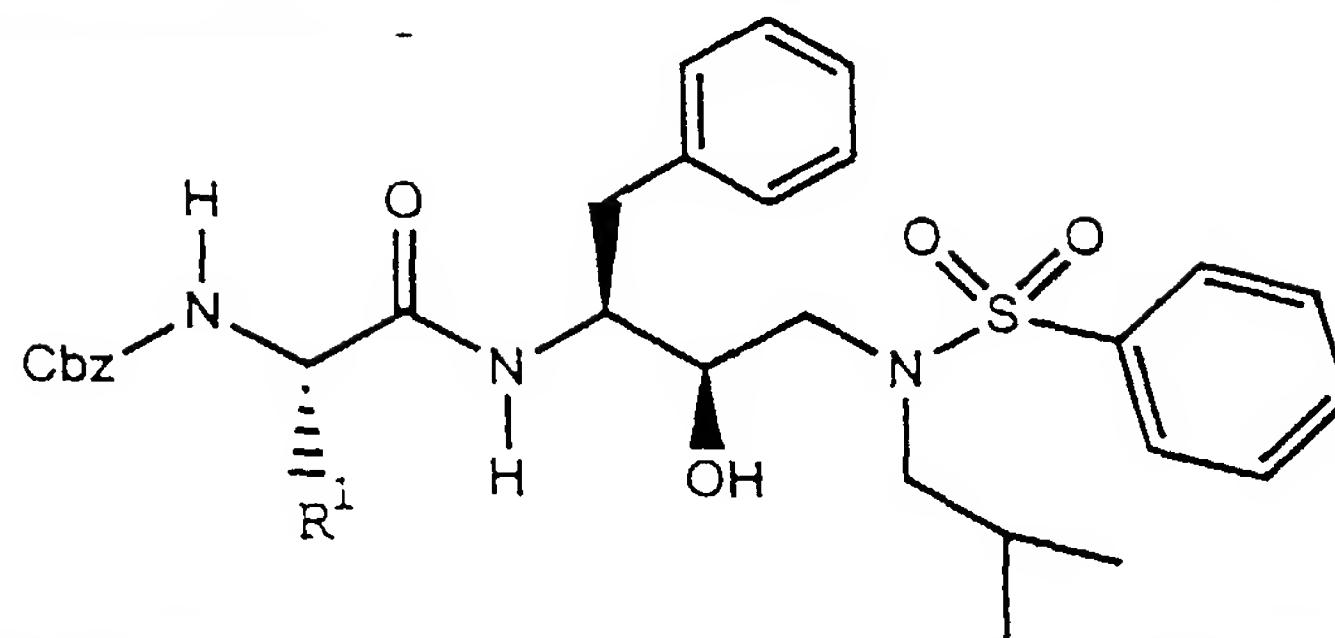
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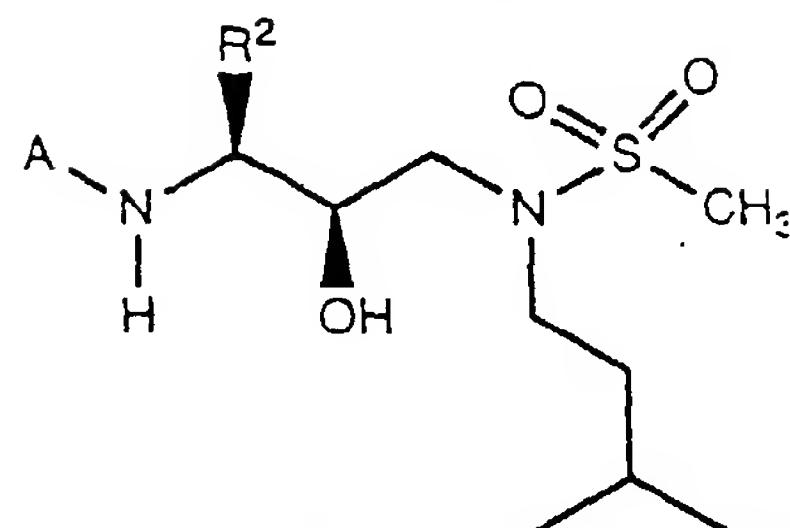
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Entry

R¹

1	CH ₂ SO ₂ CH ₃
2	(R)-CH(OH)CH ₃
3	CH(CH ₃) ₂
4	(R,S)CH ₂ SOCH ₃
5	CH ₂ SO ₂ NH ₂
6	CH ₂ SCH ₃
7	CH ₂ CH(CH ₃) ₂
8	CH ₂ CH ₂ C(O)NH ₂
9	(S)-CH(OH)CH ₃
10	-CH ₂ C≡C-H

TABLE 7

15

Entry	R ²	A
1	n-Bu	Cbz-Asn
2	cyclohexylmethyl	Cbz-Asn
3	n-Bu	BOC
4	n-Bu	Cbz
5	C ₆ H ₅ CH ₂	BOC
6	P-F-C ₆ H ₅ CH ₂	Cbz
7	C ₆ H ₅ CH ₂	benzoyl
8	cyclohexylmethyl	Cbz
9	n-Bu	Q-Asn
10	cyclohexylmethyl	Q-Asn
11	C ₆ H ₅ CH ₂	Cbz-Ile
12	C ₆ H ₅ CH ₂	Q-Ile
13	P-F-C ₆ H ₅ CH ₂	Cbz-t-BuGly
14	C ₆ H ₅ CH ₂	Q-t-BuGly
15	C ₆ H ₅ CH ₂	Cbz-Val
16	C ₆ H ₅ CH ₂	Q-Val
17	2-naphthylmethyl	Cbz-Asn
18	2-naphthylmethyl	Q-Asn
19	2-naphthylmethyl	Cbz
20	n-Bu	Cbz-Val
21	n-Bu	Q-Val
22	n-Bu	Q-Ile
23	n-Bu	Cbz-t-BuGly

TABLE 7 (Cont'd)

5

	Entry	R ²	A
10	24	n-Bu	Q-t-BuGly
	25	p-F(C ₆ H ₄)CH ₂	Q-Asn
	26	p-F(C ₆ H ₄)CH ₂	Cbz
15	27	p-F(C ₆ H ₄)CH ₂	Cbz-Asn
	28	C ₆ H ₅ CH ₂	Cbz-propargylglycine
	29	C ₆ H ₅ CH ₂	Q-propargylglycine
20	30	C ₆ H ₅ CH ₂	
		acetylpropargylglycine	

25

30

35

40

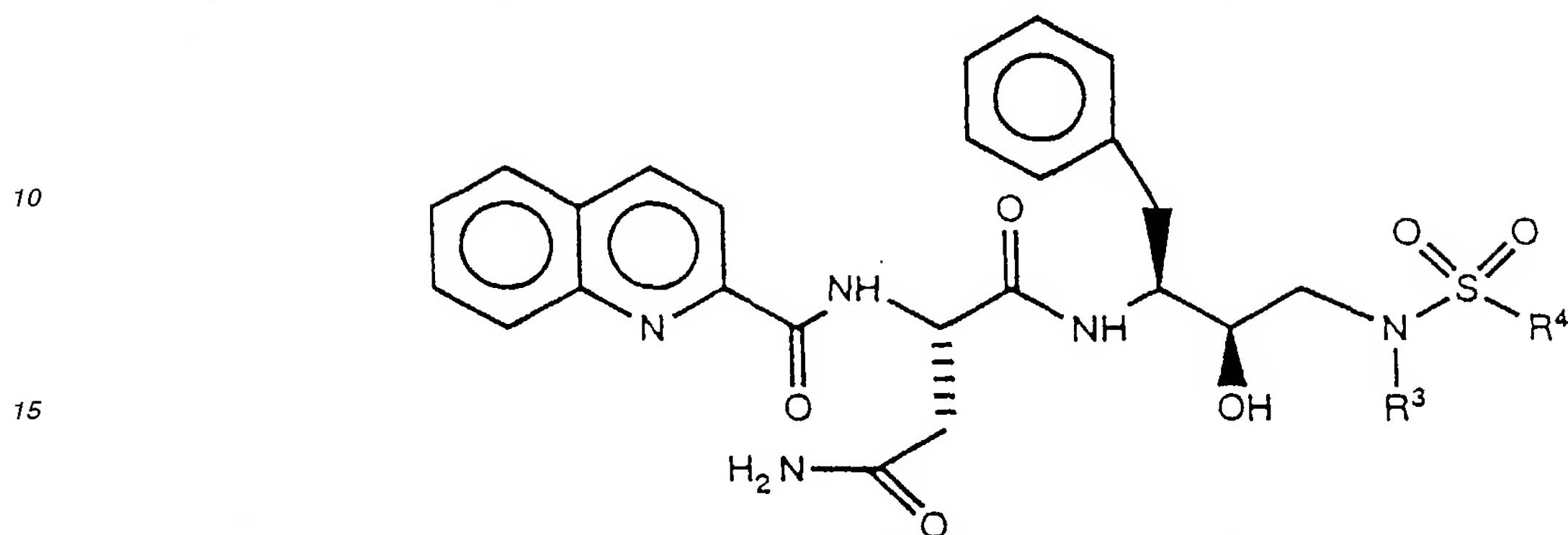
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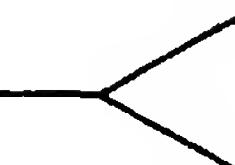
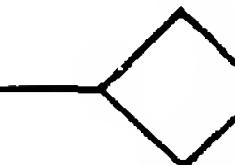
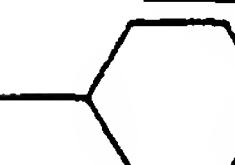
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TABLE 8

5



20

Entry	R^3	R^4
25		
30	1 $-CH_2CH(CH_3)_2$	$-C(CH_3)_2$
	2 $-CH_2CH_2CH(CH_3)_2$	
	3 $-CH_2CH_2CH_2CH(CH_3)_2$	
35	4 $-CH_2CH_2CH_2CH(CH_3)_2$	
	5 $-CH_2CH_2CH_2CH_2CH(CH_3)_2$	

45

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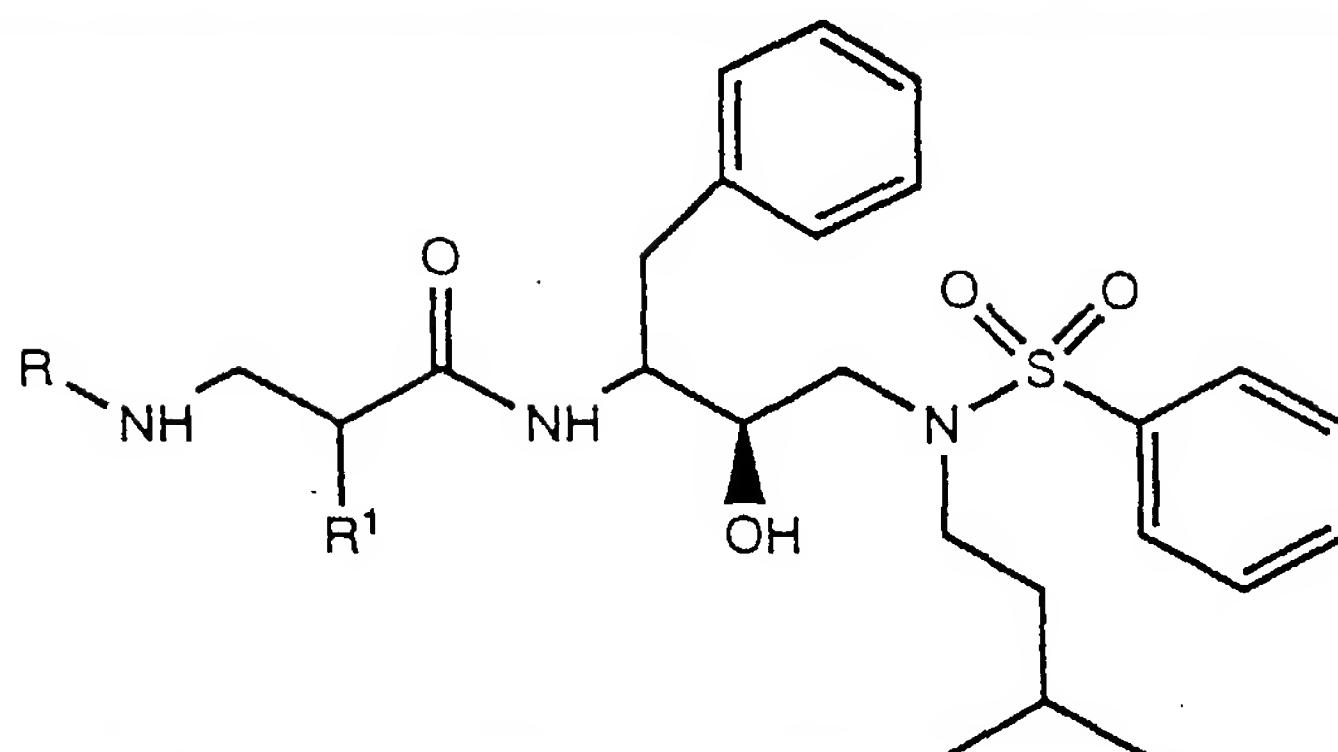
TABLE 9

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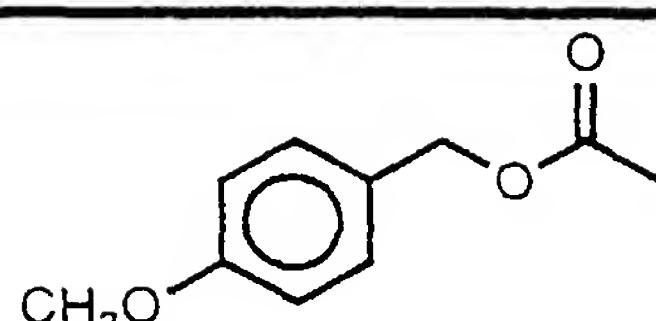
Entry

R

R¹

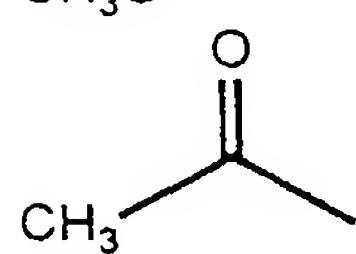
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1

-CH₃

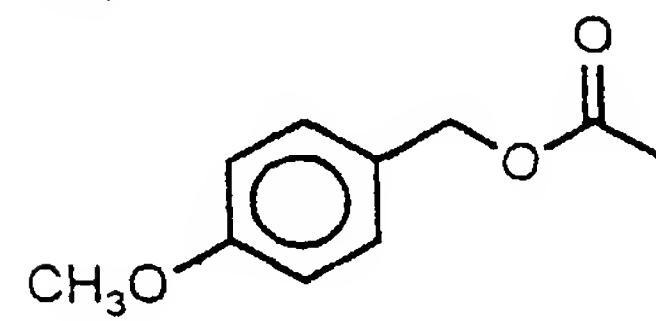
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2

-CH₃

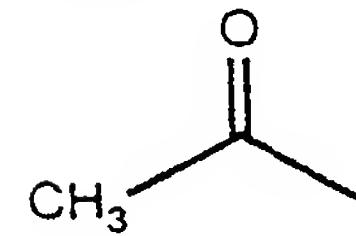
40

3

-CH(CH₃)₂

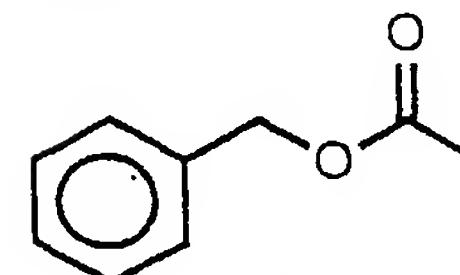
45

4

-CH(CH₃)₂

50

5

-C(CH₃)₃

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6

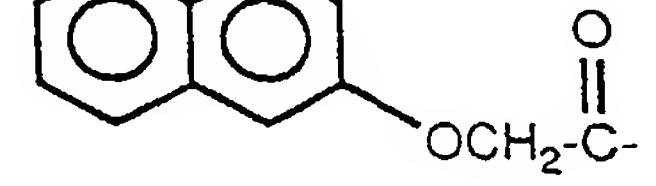
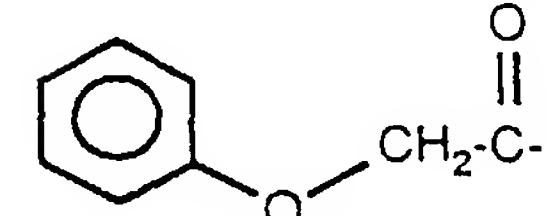
-CH₃-CH₃

Table 9 (Cont'd)

5

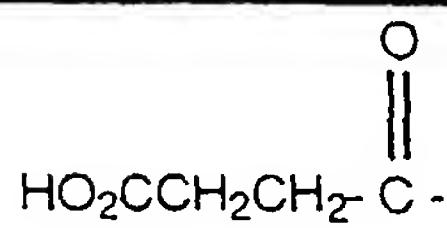
Entry

R

R¹

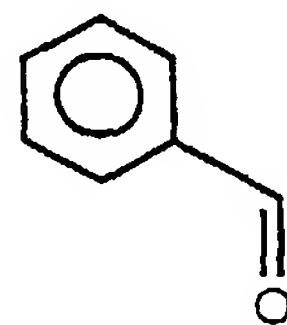
10

8

-CH₃

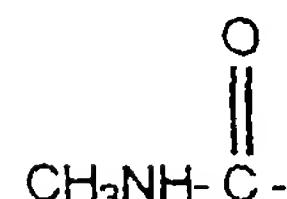
15

9

-CH₃

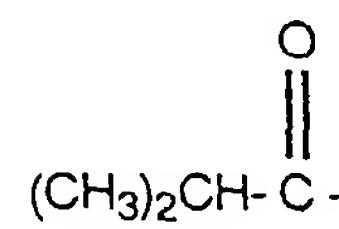
20

10

-CH₃

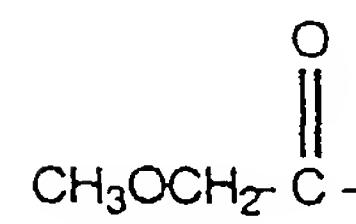
25

11

-CH₃

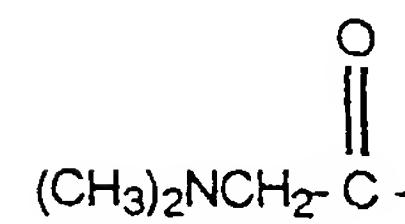
30

12

-CH₃

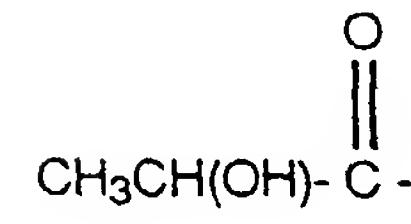
35

13

-CH₃

40

14

-CH₃

50

55

TABLE 9 (Cont'd)

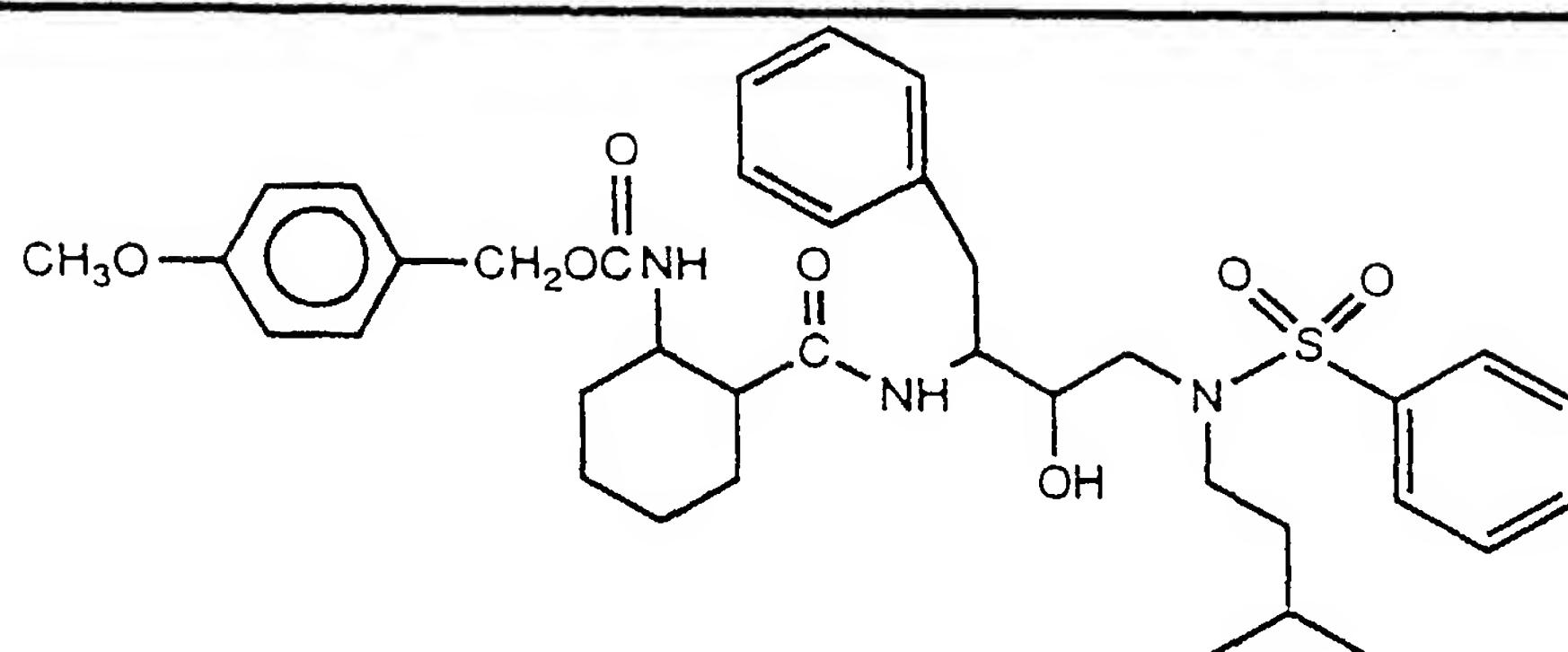
5

Entry

10

15

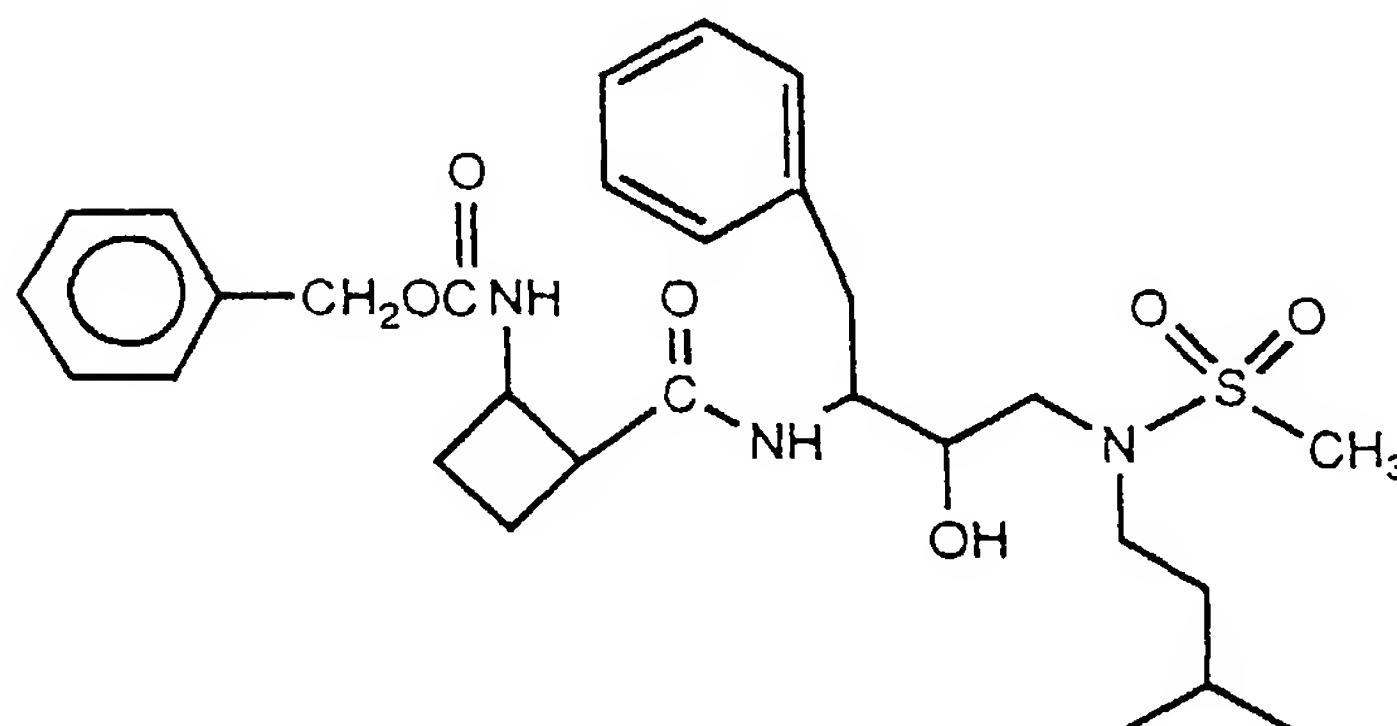
15



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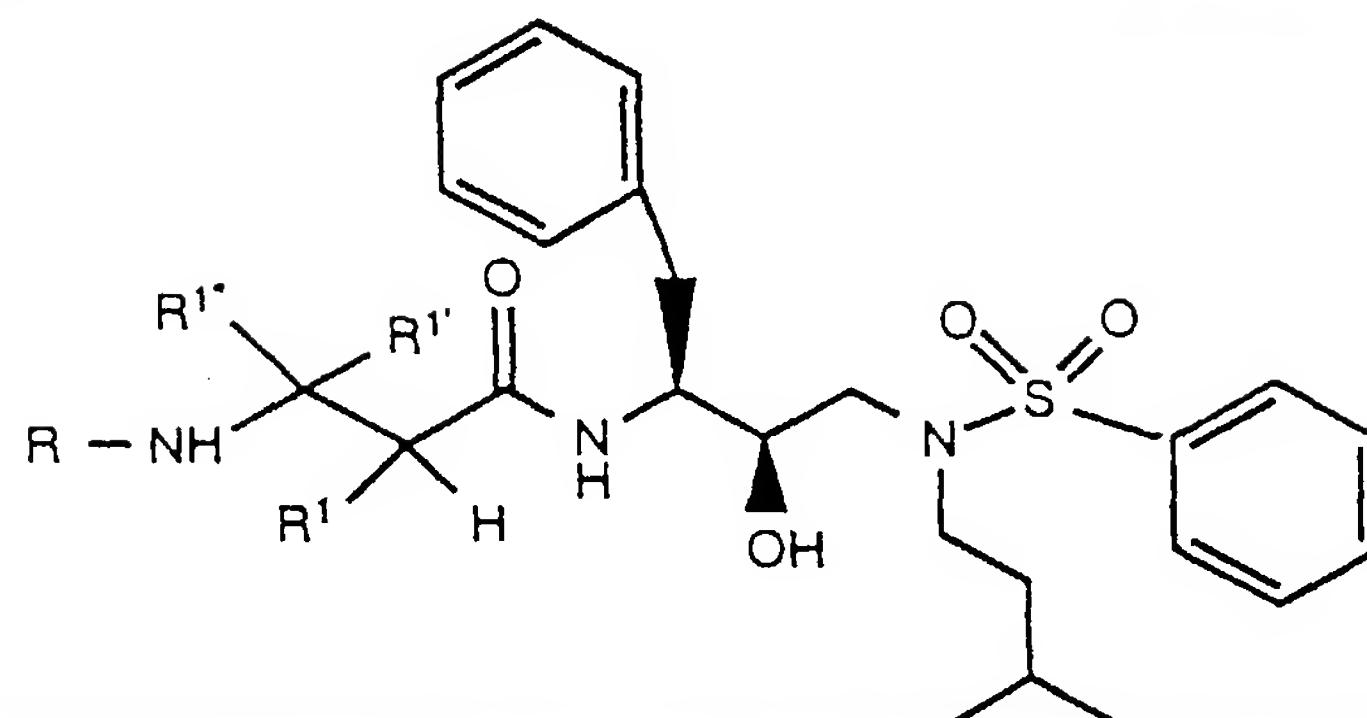
40

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TABLE 10

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45
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55Entry R¹ R^{1'} R^{1''} R

	R ¹	R ^{1'}	R ^{1''}	R
1	H	H	H	
2	H	H	H	
3	H	CH ₃	H	
4	H	CH ₃	CH ₃	
5	H	H	CO ₂ CH ₃	
6	H	H	H	
7	H	H	H	
8	H	H	CONH ₂	Cbz
9	H	H	CONH ₂	2-quinolylcarbonyl

TABLE 11

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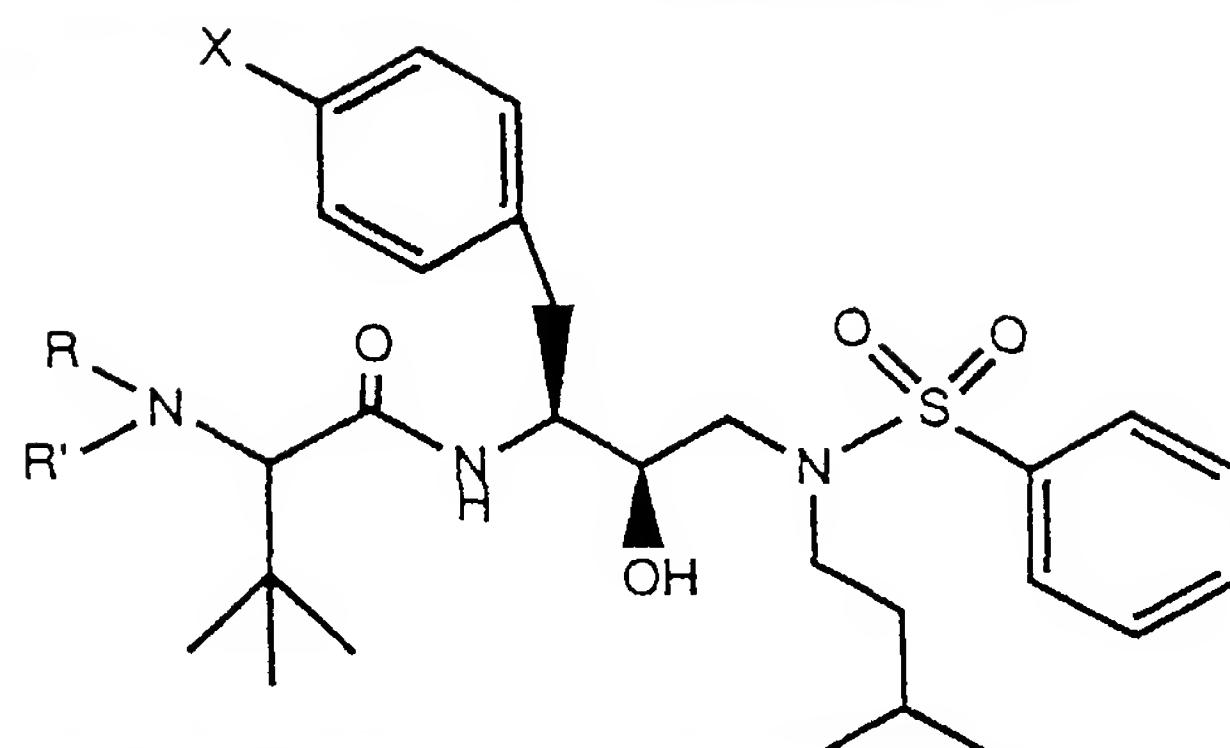
35

40

45

50

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Entry

R

R'

X

1

R=H

R'=H

X=H

2

R=Me

R'=Me

X=H

3

R=H

R'=Me

X=H

4

R=Me

R'=Me

X=F

5

R=H

R'=Me

X=F

6

R=Cbz

R'=Me

X=H

7

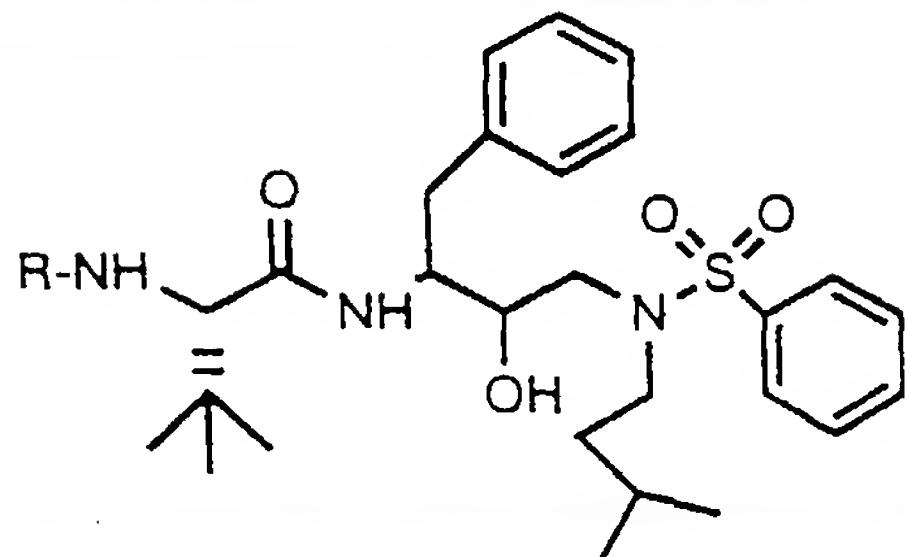
R=H

R'=Bz

X=H

8

R+R'=pyrrole X=H

TABLE 12

15

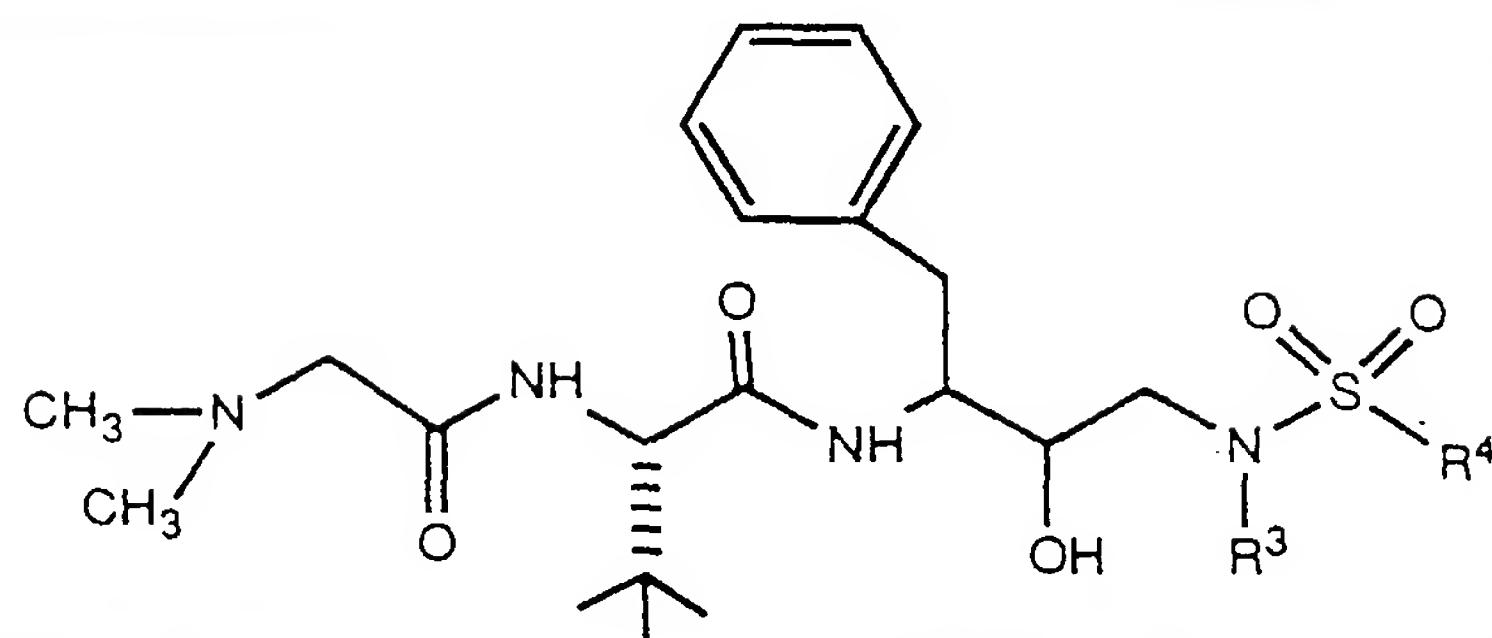
Entry	Acyl Group (R)
1	benzyloxycarbonyl
2	<u>tert</u> -butoxycarbonyl
3	acetyl
4	2-quinoylcarbonyl
5	phenoxyacetyl
6	benzoyl
7	methyloxaloyl
8	pivaloyl
9	trifluoracetyl
10	bromoacetyl
11	hydroxyacetyl
12	morpholinylacetyl
13	N,N-dimethylaminoacetyl
14	N-benzylaminoacetyl
15	N-phenylaminoacetyl
16	N-benzyl-N-methylaminoacetyl
17	N-methyl-N-(2-hydroxyethyl)aminoacetyl
18	N-methylcarbamoyl
19	3-methylbutyryl
20	N-isobutylcarbamoyl
21	succinoyl (3-carboxypropionyl)
22	carbamoyl
23	N-(2-indanyl)aminoacetyl

TABLE 13

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Entry R³R⁴

25

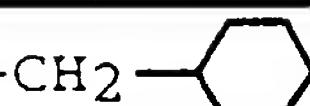
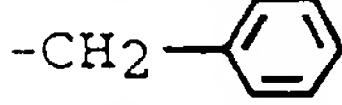
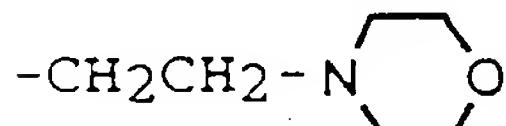
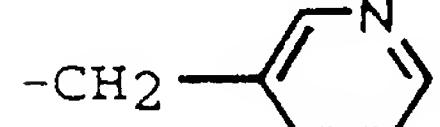
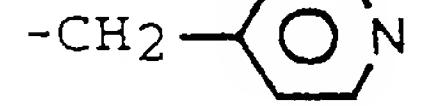
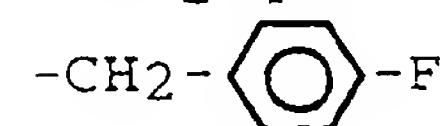
1	-CH ₃	-n-Butyl
2	-i-Butyl	-CH ₃
3	-i-Butyl	-n-Butyl
4	-i-Propyl	-n-Butyl
30	-C ₆ H ₅	-n-Butyl
5	-CH ₂ -cyclohexyl	-n-Butyl
6	-CH ₂ -phenyl	-n-Butyl
7	-CH ₂ -cyclohexyl	-n-Butyl
35	cyclohexyl	-n-Butyl
8	-i-Butyl	-n-Propyl
9	-i-Butyl	-CH ₂ CH(CH ₃) ₂
10	-i-Butyl	-n-Butyl
40	-(R)-CH(CH ₃)-phenyl	-i-Propyl
11	-CH ₂ -cyclohexyl	-CH ₂ CH ₂ CH(CH ₃) ₂
12	-CH ₂ -cyclohexyl	-CH ₂ CH ₃
45	-CH ₂ -cyclohexyl	-CH(CH ₃) ₂
13	i-Butyl	cyclohexyl
14	i-Butyl	
15	i-Butyl	
16	i-Butyl	

50

55

TABLE 13 (Cont'd).

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Entry	R ³	R ⁴
10	17 -CH ₂ - 	- (CH ₂) ₂ CH(CH ₃) ₂
	18 (CH ₂) ₂ CH(CH ₃) ₂	-CH(CH ₃) ₂
	19 i-Butyl	-CH(CH ₃) ₂
15	20 i-Butyl	-C(CH ₃) ₃
	21 -CH ₂ - 	-C(CH ₃) ₃
20	22 - (CH ₂) ₂ CH(CH ₃) ₂	-C(CH ₃) ₃
	23 -CH ₂ C ₆ H ₅	-C(CH ₃) ₃
	24 - (CH ₂) ₂ C ₆ H ₅	-C(CH ₃) ₃
25	25 n-Butyl	-C(CH ₃) ₃
	26 n-Pentyl	-C(CH ₃) ₃
30	27 n-Hexyl	-C(CH ₃) ₃
	28 -CH ₂ - 	-C(CH ₃) ₃
35	29 -CH ₂ C(CH ₃) ₃	-C(CH ₃) ₃
	30 -CH ₂ CH ₂ -N 	-C(CH ₃) ₃
40	31 -CH ₂ C ₆ H ₅ OCH ₃ (para)	-C(CH ₃) ₃
	32 -CH ₂ - 	-C(CH ₃) ₃
	33 -CH ₂ - 	-C(CH ₃) ₃
45	34 - (CH ₂) ₂ C(CH ₃) ₃	-C(CH ₃) ₃
	35 - (CH ₂) ₄ OH	-C(CH ₃) ₃
	36 -CH ₂ - 	-C(CH ₃) ₃

50

55

TABLE 13 (Cont'd)

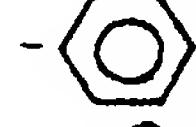
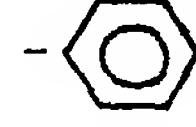
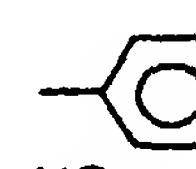
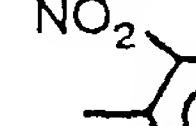
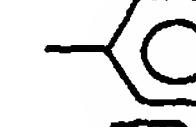
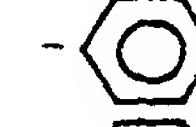
Entry	R ³	R ⁴
37	-CH ₂ -	-C(CH ₃) ₃
38	-CH ₂ CH(CH ₃) ₂	-C ₆ H ₅
39	i-amyl	-CH ₂ C(CH ₃) ₃
40		-CH ₂ C(CH ₃) ₃
41		-CH ₂ C(CH ₃) ₃
42	i-butyl	-CH ₂ C(CH ₃) ₃
43	-CH ₂ Ph	-Ph
44	-CH ₂ -	-Ph
45	-CH ₂ -	-Ph
46	-CH ₂ -	-Ph
47	-CH ₂ -	-Ph
48	-CH ₂ -	-Ph
49	-CH ₂ CH=CH ₂	-Ph
50		-Ph
51		-Ph
52	-CH ₂ CH ₂ Ph	-Ph
53	-CH ₂ CH ₂ CH ₂ CH ₂ OH	-Ph
54	-CH ₂ CH ₂ N(CH ₃) ₂	-Ph
55	-CH ₂ CH ₂ -N	-Ph
56	-CH ₃	-Ph

45

50

55

TABLE 13 (Cont'd)

Entry	R ³	R ⁴
57	-CH ₂ CH ₂ CH ₂ SCH ₃	-Ph
58	-CH ₂ CH ₂ CH ₂ S(O)C ₂ H ₅	-Ph
59	-CH ₂ CH ₂ CH(CH ₃) ₂	- 
60	-CH ₂ CH ₂ CH(CH ₃) ₂	-CH ₂ - 
61	-CH ₂ CH ₂ CH(CH ₃) ₂	-CH ₂ CH ₂ CH ₃
62	-CH ₂ CH ₂ CH(CH ₃) ₂	-CH ₃
63	-CH ₂ CH ₂ CH(CH ₃) ₂	-  -F
64	-CH ₂ CH ₂ CH(CH ₃) ₂	- 
65	-CH ₂ CH ₂ CH(CH ₃) ₂	-  -NO ₂
66	-CH ₂ CH ₂ CH(CH ₃) ₂	- 
67	-CH ₂ CH ₂ CH(CH ₃) ₂	-  -OCH ₃
68	-CH ₂ CH ₂ CH(CH ₃) ₂	-  -NO ₂
69	-CH ₂ CH ₂ CH(CH ₃) ₂	-  -NO ₂
70	-CH ₂ CH ₂ CH(CH ₃) ₂	-  -CF ₃
71	-CH ₂ CH ₂ CH(CH ₃) ₂	-  -NHAc
72	-CH ₂ CH ₂ CH(CH ₃) ₂	-  -Cl

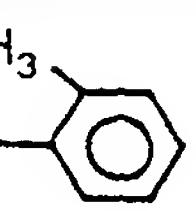
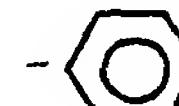
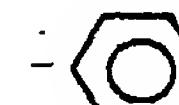
45

50

55

TABLE 13 (Cont'd)

5

	Entry	R ³	R ⁴
10	73	-CH ₂ CH ₂ CH(CH ₃) ₂	-  -CH ₃
	74	-CH ₂ CH ₂ CH(CH ₃) ₂	CO ₂ CH ₃ 
15	75	-CH ₂ CH(CH ₃) ₂	- 
	76	-CH ₂ CH(CH ₃) ₂	- 
20	77	-CH ₂ CH(CH ₃) ₂	- 
	78	-CH ₂ CH(CH ₃) ₂	- 
25	79	-CH ₂ CH ₂ CH ₃	- 
	80	-CH ₂ CH ₂ CH ₂ CH ₃	- 

30

a benzylloxycarbonyl

35

b 2-quinolinylcarbonyl

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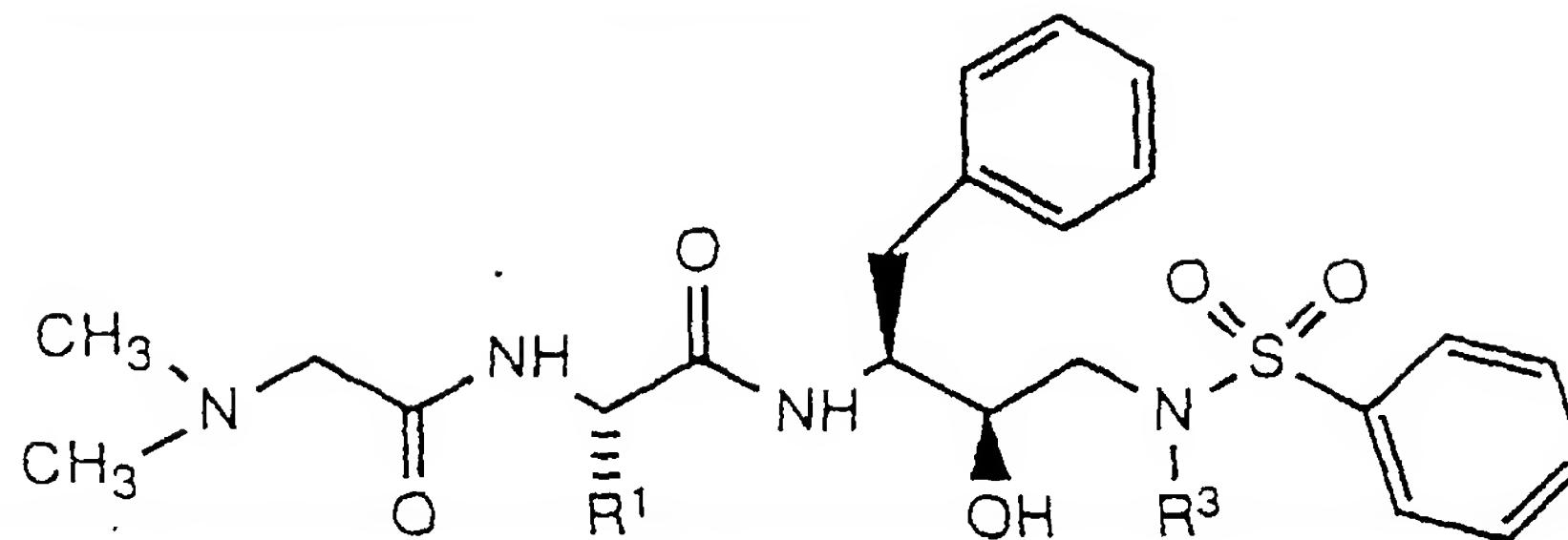
55

Table 14

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Entry

R¹R³

25

1

C(CH₃)₃CH₂CH₂CH(CH₃)₂

2

CH₂C≡CHCH₂CH₂CH(CH₃)₂

3

C(CH₃)₂(SCH₃)CH₂CH₂CH(CH₃)₂

4

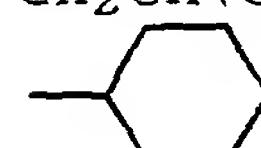
C(CH₃)₂(S[O]CH₃)CH₂CH₂CH(CH₃)₂

30

5

C(CH₃)₂(S[O]₂CH₃)CH₂CH₂CH(CH₃)₂

6

C(CH₃)₃CH₂CH(CH₃)₂

7

C(CH₃)₃CH₂CH(CH₃)₂

35

8

CH(CH₃)₂CH₂CH(CH₃)₂

9

CH(CH₂CH₃)(CH₃)CH₂CH(CH₃)₂

40

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50

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Table 14A

5

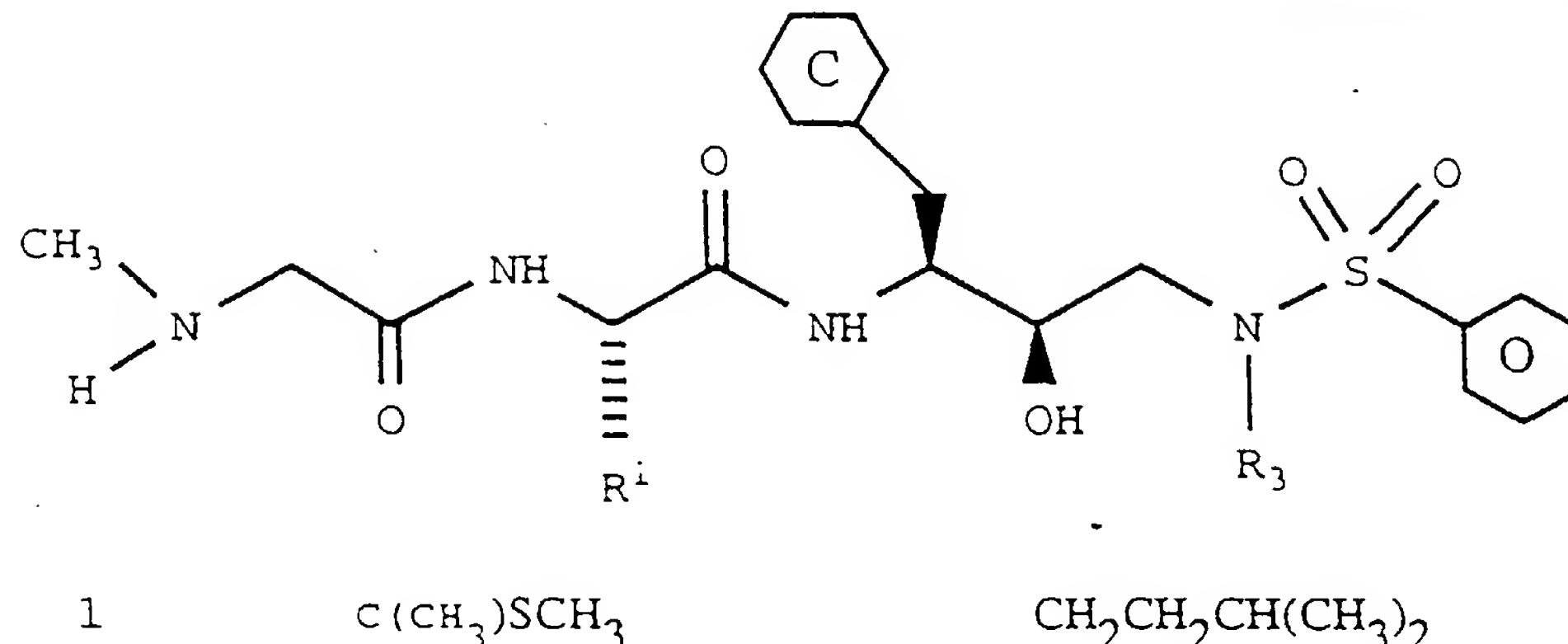
Entry

10

15

20

25

Example 17

The compounds of the present invention are effective HIV protease inhibitors. Utilizing an enzyme assay as described below, the compounds set forth in the examples herein disclosed inhibited the HIV enzyme. The preferred compounds of the present invention and their calculated IC_{50} (inhibiting concentration 50%, i.e., the concentration at which the inhibitor compound reduces enzyme activity by 50%) values are shown in Table 16. The enzyme method is described below. The substrate is 2-Ile-Nle-Phe(p-NO₂)-Gln-ArgNH₂. The positive control is MVT-101 (Miller, M. et al, *Science*, 246, 1149 (1989)] The assay conditions are as follows:

35 Assay buffer: 20 mM sodium phosphate, pH 6.4
 20% glycerol
 1 mM EDTA
 1 mM DTT
 0.1% CHAPS

40 The above described substrate is dissolved in DMSO, then diluted 10 fold in assay buffer. Final substrate concentration in the assay is 80 μM .

HIV protease is diluted in the assay buffer to a final enzyme concentration of 12.3 nanomolar, based on a molecular weight of 10,780.

45 The final concentration of DMSO is 14% and the final concentration of glycerol is 18%. The test compound is dissolved in DMSO and diluted in DMSO to 10x the test concentration; 10 μl of the enzyme preparation is added, the materials mixed and then the mixture is incubated at ambient temperature for 15 minutes. The enzyme reaction is initiated by the addition of 40 μl of substrate. The increase in fluorescence is monitored at 4 time points (0, 8, 16 and 24 minutes) at ambient Temperature. Each assay is carried out in duplicate wells.

50 The preceding examples can be repeated with similar success by substituting the generically or specifically described reactants and/or operating conditions of this invention for those used in the preceding examples.

55

TABLE 15A

5

Entry	Compound	IC50 (nanomolar)
10 15 20 25 30 35 40		1.5
2		1.4
3		27

45

50

55

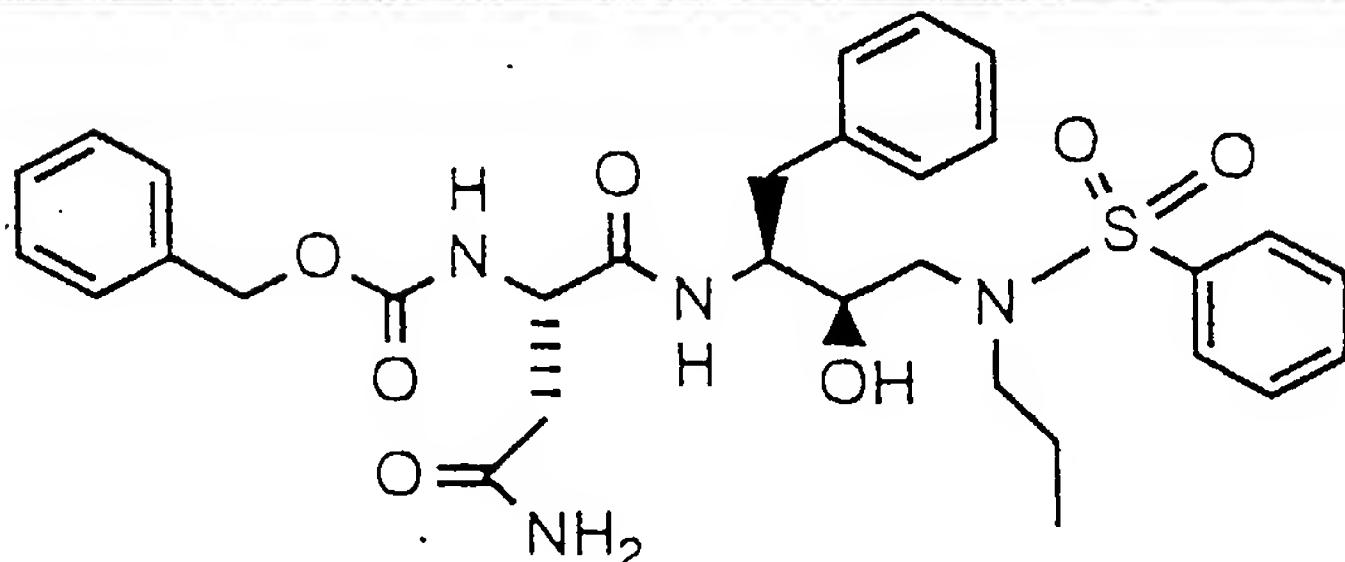
TABLE 15A (Cont'd)

5

Entry Compound IC₅₀ (nanomolar)

10

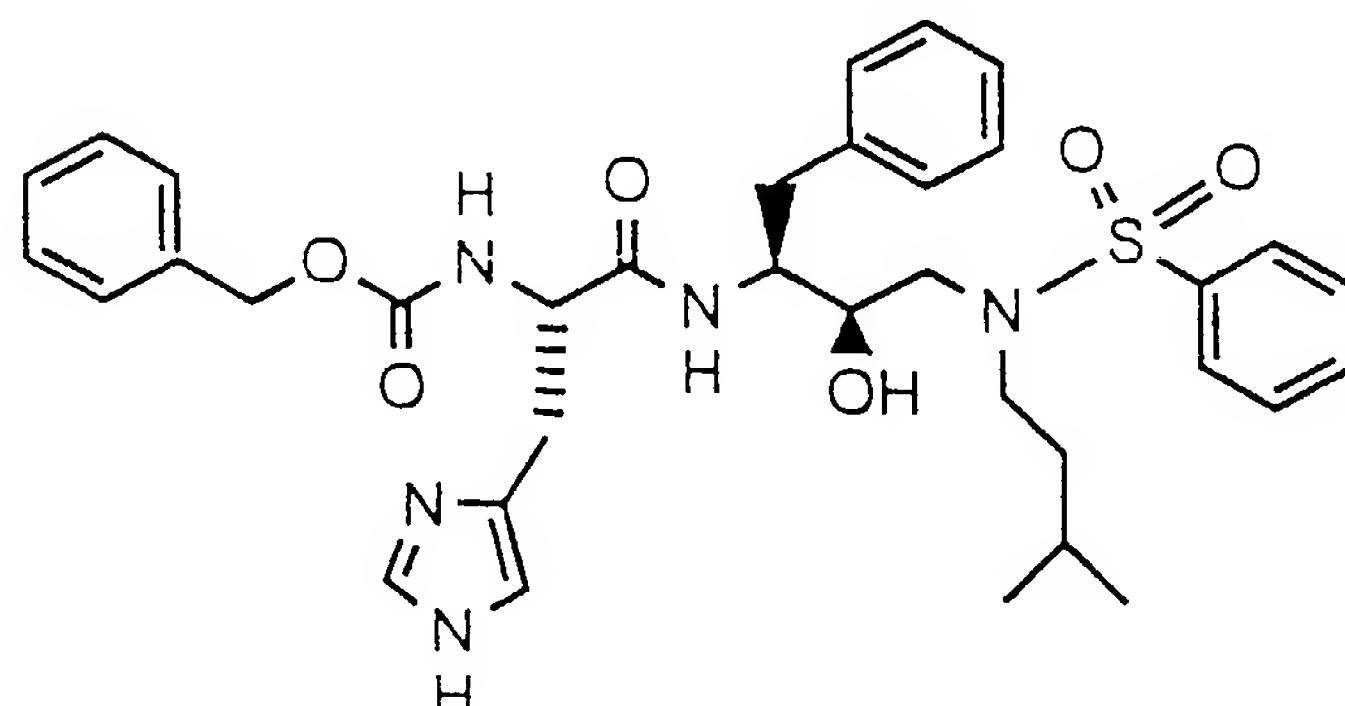
4



3.6

15

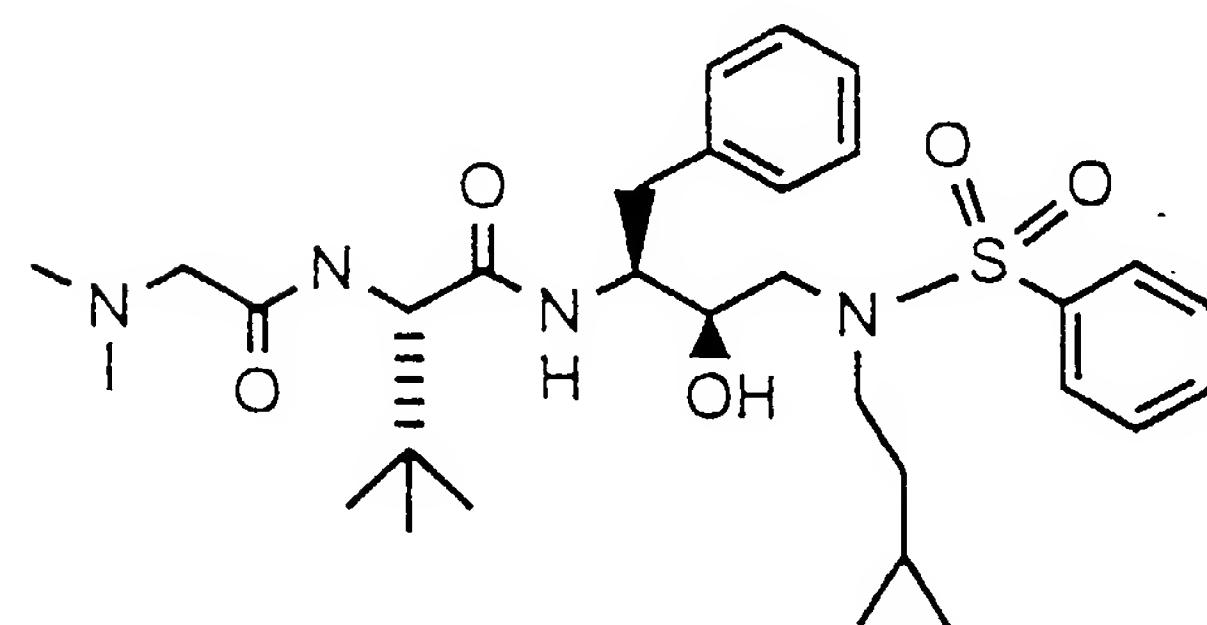
5



4.2

20

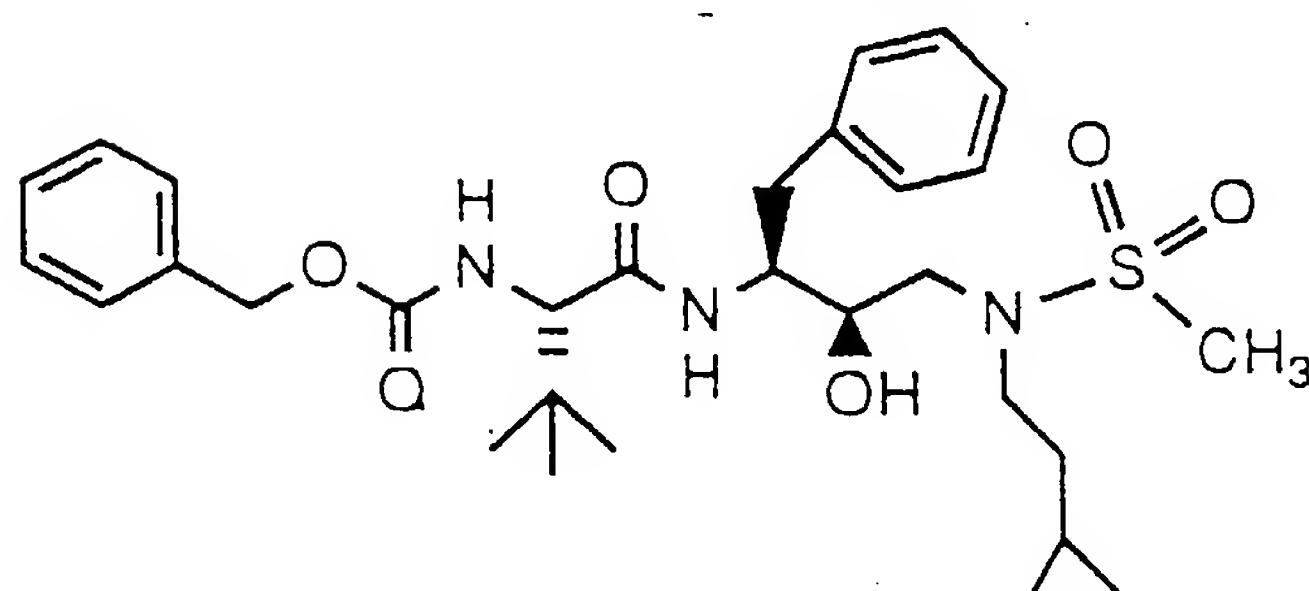
6



3.5

25

7



81

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TABLE 15B

Ex.	Table	Entry	IC ₅₀ (μM) or % inhib
16	3	1	0.081

TABLE 15B (continued)

Ex.	Table	Entry	IC ₅₀ (uM) or % inhib
5	16	3	38% @ 0.1 uM, 90% @ 1.0 uM
10	16	3	0.0024
15	16	3	0.0018
20	16	3	0.003
25	16	3	0.0025
30	16	3	0.0016
35	16	4	0.0015
40	16	5	0.0014
45	16	5	0.0022
50	16	5	0.0018
55	16	5	0.0044
60	16	5	0.0020
65	16	7	0.0028
70	16	7	0.0015
75	16	11	0.13
80	16	11	41% @ 0.1 uM, 86% @ 1 uM
85	16	12	0.0033
90	16	14	0.0049
95	16	14	0.0032

Example 18

The effectiveness of the compounds listed in Table 15 were determined in the above-described enzyme assay and in a CEM cell assay.

The HIV inhibition assay method of acutely infected cells is an automated tetrazolium based colorimetric assay essentially that reported by Pauwles et al, *J. Virol. Methods*, 20, 309-321 (1988). Assays were performed in 96-well tissue culture plates. CEM cells, a CD4+ cell line, were grown in RPMI-1640 medium (Gibco) supplemented with a 10% fetal calf serum and were then treated with polybrene (2μg/ml). An 80 μl volume of medium containing 1 x 10⁴ cells was dispensed into each well of the tissue culture plate. To each well was added a 100μl volume of test compound dissolved in tissue culture medium (or medium without test compound as a control) to achieve the desired final concentration and the cells were incubated at 37°C for 1 hour. A frozen culture of HIV-1 was diluted in culture medium to a concentration of 5 x 10⁴ TCID₅₀ per ml (TCID₅₀ = the dose of virus that infects 50% of cells in tissue culture), and a 20μL volume of the virus sample (containing 1000 TCID₅₀ of virus) was added to wells containing test compound and to wells containing only medium (infected control cells). Several wells received culture medium without virus (uninfected control cells). Likewise, the intrinsic toxicity of the test compound was determined by adding medium without virus to several wells containing test compound. In summary, the tissue culture plates contained the following experiments:

	Cells	Drug	Virus
1.	+	-	-
2.	+	+	-
3.	+	-	+
4.	+	+	+

In experiments 2 and 4 the final concentrations of test compounds were 1, 10, 100 and 500 μg/ml. Either azidothymidine (AZT) or dideoxyinosine (ddl) was included as a positive drug control. Test compounds were dissolved in DMSO and diluted into tissue culture medium so that the final DMSO concentration did not exceed 1.5% in any case. DMSO was added to all control wells at an appropriate concentration.

Following the addition of virus, cells were incubated at 37°C in a humidified, 5% CO₂ atmosphere for 7 days. Test compounds could be added on days 0, 2 and 5 if desired. On day 7, post-infection, the cells in each well were resuspended and a 100μl sample of each cell suspension was removed for assay. A 20μL volume of a 5 mg/ml solution of 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) was added to each 100μL cell suspension, and the cells were incubated for 4 hours at 27°C in a 5% CO₂ environment. During this incubation, MTT is metabolically reduced

by living cells resulting in the production in the cell of a colored formazan product. To each sample was added 100 μ l of 10% sodium dodecylsulfate in 0.01 N HCl to lyse the cells, and samples were incubated overnight. The absorbance at 590 nm was determined for each sample using a Molecular Devices microplate reader. Absorbance values for each set of wells is compared to assess viral control infection, uninfected control cell response as well as test compound by cytotoxicity and antiviral efficacy.

TABLE 16

Entry	Compound	IC ₅₀ (nm)	EC ₅₀ (nm)	TD ₅₀ (nm)
1		1	5	203
2		1	11	780
3		27	64	28

TABLE 16 (Cont'd)

5

Entry	Compound	IC ₅₀ (nm)	EC ₅₀ (nm)	TD ₅₀ (nm)
10		>100	380	425
15		3	25	39
20				
25		3	11	54
30				
35		2	12	7.5
40				
45				
50				

55

TABLE 16 (Conc 'á)

5

Entry	Compound	IC ₅₀ (nm)	EC ₅₀ (nm)	TD ₅₀ (nm)
10				
15	8			
		3	<16	
20				
25	9			
		4	15	55,000
30				
35				
40	10			
		5	38	

45 The compounds of the present invention are effective antiviral compounds and, in particular, are effective retroviral inhibitors as shown above. Thus, the subject compounds are effective HIV protease inhibitors. It is contemplated that the subject compounds will also inhibit other retroviruses such as other lentiviruses in particular other strains of HIV, e.g. HIV-2, human T-cell leukemia virus, respiratory syncitial virus, simia immunodeficiency virus, feline leukemia virus, feline immuno-deficiency virus, hepadnavirus, cytomegalovirus and picornavirus. Thus, the subject compounds are effective in the treatment and/or prophylaxis of retroviral infections.

50 Compounds of the present invention can possess one or more asymmetric carbon atoms and are thus capable of existing in the form of optical isomers as well as in the form of racemic or nonracemic mixtures thereof. The optical isomers can be obtained by resolution of the racemic mixtures according to conventional processes, for example by formation of diastereoisomeric salts by treatment with an optically active acid or base. Examples of appropriate acids 55 are tartaric, diacetyl tartaric, dibenzoyl tartaric, ditoluoyl tartaric and camphorsulfonic acid and then separation of the mixture of diastereoisomers by crystallization followed by liberation of the optically active bases from these salts. A different process for separation of optical isomers involves the use of a chiral chromatography column optimally chosen to maximize the separation of the enantiomers. Still another available method involves synthesis of covalent diaster-

5 eoisomeric molecules by reacting compounds of Formula I with an optically pure acid in an activated form or an optically pure isocyanate. The synthesized diastereoisomers can be separated by conventional means such as chromatography, distillation, crystallization or sublimation, and then hydrolyzed to deliver the enantiomerically pure compound. The optically active compounds of Formula I can likewise be obtained by utilizing optically active starting materials. These isomers may be in the form of a free acid, a free base, an ester or a salt.

10 The compounds of the present invention can be used in the form of salts derived from inorganic or organic acids. These salts include but are not limited to the following: acetate, adipate, alginate, citrate, aspartate, benzoate, benzene sulfonate, bisulfate, butyrate, camphorate, camphorsulfonate, digluconate, cyclopentanepropionate, dodecylsulfate, ethanesulfonate, glucoheptanoate, glycerophosphate, hemisulfate, heptanoate, hexanoate, fumarate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxy-ethanesulfonate, lactate, maleate, methanesulfonate, nicotinate, 2-naphthalenesulfonate, oxalate, palmoate, pectinate, persulfate, 3-phenylpropionate, picrate, pivalate, propionate, succinate, tartrate', thiocyanate, tosylate, mesylate and undecanoate. Also, the basic nitrogen-containing groups can be quaternized with such agents as lower alkyl halides, such as methyl, ethyl, propyl, and butyl chloride, bromides, and iodides; dialkyl sulfates like dimethyl, diethyl, dibutyl, and diamyl sulfates, long chain halides such as decyl, lauryl, myristyl and stearyl chlorides, bromides and iodides, aralkyl halides like benzyl and phenethyl bromides, and others. Water or oil-soluble or dispersible products are thereby obtained.

15 Examples of acids which may be employed to form pharmaceutically acceptable acid addition salts include such inorganic acids as hydrochloric acid, sulphuric acid and phosphoric acid and such organic acids as oxalic acid, maleic acid, succinic acid and citric acid. Other examples include salts with alkali metals or alkaline earth metals, such as sodium, potassium, calcium or magnesium or with organic bases.

20 Total daily dose administered to a host in single or divided doses may be in amounts, for example, from 0.001 to 10 mg/kg body weight daily and more usually 0.01 to 1 mg. Dosage unit compositions may contain such amounts of submultiples thereof to make up the daily dose.

25 The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration.

30 The dosage regimen for treating a disease condition with the compounds and/or compositions of this invention is selected in accordance with a variety of factors, including the type, age, weight, sex, diet and medical condition of the patient, the severity of the disease, the route of administration, pharmacological considerations such as the activity, efficacy, pharmacokinetic and toxicology profiles of the particular compound employed, whether a drug delivery system is utilized and whether the compound is administered as part of a drug combination. Thus, the dosage regimen actually employed may vary widely and therefore may deviate from the preferred dosage regimen set forth above.

35 The compounds of the present invention may be administered orally, parenterally, by inhalation spray, rectally, or topically in dosage unit formulations containing conventional nontoxic pharmaceutically acceptable carriers, adjuvants, and vehicles as desired. Topical administration may also involve the use of transdermal administration such as transdermal patches or iontophoresis devices. The term parenteral as used herein includes subcutaneous injections, intravenous, intramuscular, intrasternal injection, or infusion techniques.

40 Injectable preparations, for example, sterile injectable aqueous or oleaginous suspensions may be formulated according to the known art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution or suspension in a nontoxic parenterally acceptable diluent or solvent, for example, as a solution in 1,3-butanediol.. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution, and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

45 Suppositories for rectal administration of the drug can be prepared by mixing the drug with a suitable nonirritating excipient such as cocoa butter and polyethylene glycols which are solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum and release the drug.

50 Solid dosage forms for oral administration may include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the active compound may be admixed with at least one inert diluent such as sucrose lactose or starch. Such dosage forms may also comprise, as in normal practice, additional substances other than inert diluents, e.g., lubricating agents such as magnesium stearate. In the case of capsules, tablets, and pills, the dosage forms may also comprise buffering agents. Tablets and pills can additionally be prepared with enteric coatings.

55 Liquid dosage forms for oral administration may include pharmaceutically acceptable emulsions, solutions, suspensions, syrups, and elixirs containing inert diluents commonly used in the art, such as water. Such compositions may also comprise adjuvants, such as wetting agents, emulsifying and suspending agents, and sweetening, flavoring, and perfuming agents.

While the compounds of the invention can be administered as the sole active pharmaceutical agent, they can also be used in combination with one or more immunomodulators, antiviral agents or other antiinfective agents. For example, the compounds of the invention can be administered in combination with AZT, DDI, DDC or with glucosidase inhibitors,

such as N-butyl-1-deoxyojirimycin or prodrugs thereof, for the prophylaxis and/or treatment of AIDS. When administered as a combination, the therapeutic agents can be formulated as separate compositions which are given at the same time or different times, or the therapeutic agents can be given as a single composition.

The foregoing is merely illustrative of the invention.

Variations and changes which are obvious to one skilled in the art are intended to be within the scope and nature of the invention which are defined in the appended claims.

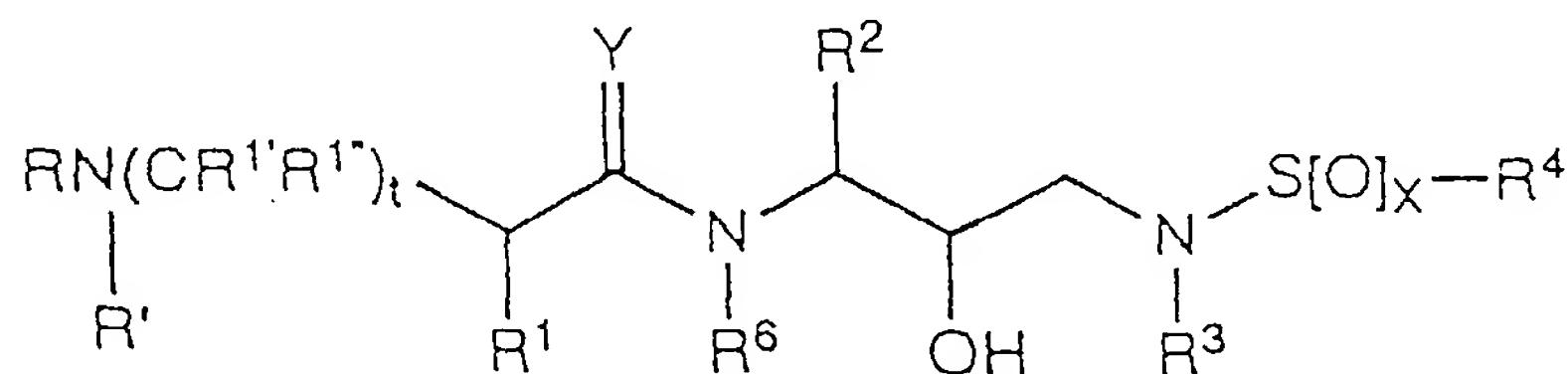
From the foregoing description, one skilled in the art can easily ascertain the essential characteristics of this invention,

10

Claims

1. A compound represented by the formula:

15



20

or a pharmaceutically acceptable salt, prodrug or ester thereof wherein:

25

R represents hydrogen, alkoxycarbonyl, aralkoxycarbonyl, alkylcarbonyl, cycloalkylcarbonyl, cycloalkylalkoxycarbonyl, cycloalkylalkanoyl, alkanoyl, aralkanoyl, aroyl, aryloxycarbonyl, aryloxycarbonylalkyl, aryloxylalkanoyl, heterocyclcarbonyl, heterocycloxycarbonyl, heterocyclalkanoyl, heterocyclalkoxycarbonyl, heteroaralkanoyl, heteroaralkoxycarbonyl, heteroaryloxy-carbonyl, heteroaroyl, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, aralkyl, aryloxyalkyl, heteroaryloxyalkyl, hydroxylalkyl, aminocarbonyl, aminoalkanoyl, and mono- and disubstituted aminocarbonyl and mono- and disubstituted aminoalkanoyl radicals wherein the substituents are selected from alkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroaralkyl, heterocycloalkyl, heterocycloalkyl radicals, or wherein said aminocarbonyl and aminoalkanoyl radicals are disubstituted, said substituents along with the nitrogen atom to which they are attached form a heterocycloalkyl or heteroaryl radical;

30

35

R' represents hydrogen and radicals as defined for R³ or R"SO₂- wherein R" represents radicals as defined for R³; or R and R' together with the nitrogen to which they are attached represent heterocycloalkyl and heteroaryl radical;

40

R¹ represents hydrogen, -CH₂SO₂NH₂, -CH₂CO₂CH₃, -CO₂CH₃, -CONH₂, -CH₂C(O)NHCH₃, -C(CH₃)₂(SH), -C(CH₃)₂(SCH₃), -C(CH₃)₂(S[O]CH₃), -C(CH₃)₂(S[O]₂CH₃), alkyl, haloalkyl, alkenyl, alkynyl and cycloalkyl radicals, and amino acid side chains selected from asparagine, S-methyl cysteine and the sulfoxide (SO) and sulfone (SO₂) derivatives thereof, isoleucine, allo-isoleucine, alanine, leucine, tert-leucine, phenylalanine, ornithine, histidine, norleucine, glutamine, threonine, glycine, allo-threonine, serine, O-alkyl serine, aspartic acid, beta-cyano alanine and valine side chains;

45

R^{1'} and R^{1''} independently represent hydrogen and radicals as defined for R¹, or one of R^{1'} and R^{1''}, together with R¹ and the carbon atoms to which R¹, R^{1'} and R^{1''} are attached, represent a cycloalkyl radical;

50

R² represents alkyl, aryl, cycloalkyl, cycloalkylalkyl and aralkyl radicals, which radicals are optionally substituted with a group selected from alkyl and halogen radicals, -NO₂, -C≡N, CF₃, -OR⁹, -SR⁹, wherein R⁹ represents hydrogen and alkyl radicals;

55

R³ represents hydrogen, alkyl, haloalkyl, alkenyl, alkynyl, hydroxylalkyl, alkoxyalkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heteroaryl, heterocycloalkylalkyl, aryl, aralkyl, heteroaralkyl, aminoalkyl and mono- and disubstituted aminoalkyl radicals, wherein said substituents are selected from alkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroaralkyl, heterocycloalkyl, and heterocycloalkylalkyl radicals, or in the case of

a disubstituted aminoalkyl radical, said substituents along with the nitrogen atom to which they are attached, form a heterocycloalkyl or a heteroaryl radical;

5 R⁴ represents radicals as defined by R³ except for hydrogen;

R⁶ represents hydrogen and alkyl radicals;

x represents 0, 1, or 2;

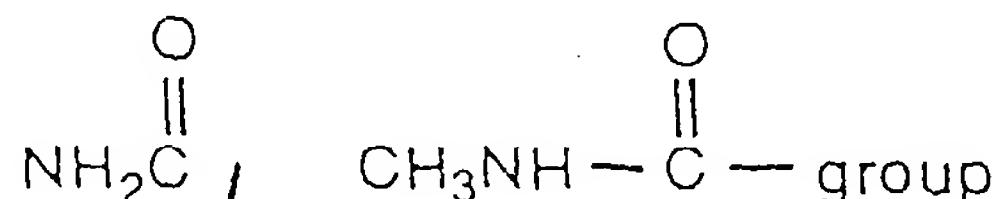
10 t represents either 0 or 1; and

Y represents O, S and NR¹⁵ wherein R¹⁵ represents hydrogen and radicals as defined for R³.

- 2. Compound according to Claim 1 wherein t is 0, Y is O, x is 2, R⁶ = hydrogen and with R' as in Claim 1 except R" SO₂, with R¹ as defined in Claim 1 except O-alkylserine being replaced by O-methylserine, with R³ as in Claim 1 except hydrogen, with R, R² and R⁴ as defined in Claim 1.
- 3. Compound of Claim 2 wherein R represents aralkoxycarbonyl and heteroaroyl radicals.
- 4. Compound of Claim 2 wherein R represents carbobenzoxy, 2-benzofurancarbonyl and 2-quinolinylcarbonyl radicals.
- 5. Compound of Claim 2 wherein R¹ represents alkyl, alkynyl and alkenyl radicals, and amino acid side chains selected from the group consisting of asparagine, valine, threonine, allo-threonine, isoleucine, S-methyl cysteine and the sulfone and sulfoxide derivatives thereof, alanine, and allo-isoleucine.
- 6. Compound of Claim 2 wherein R¹ represents methyl, propargyl, t-butyl, isopropyl and sec-butyl radicals, and amino acid side chains selected from the group consisting of asparagine, valine, S-methyl cysteine, allo-iso-leucine, iso-leucine, threonine, serine, aspartic acid, beta-cyano alanine, and allo-threonine side chains.
- 7. Compound of Claim 2 wherein R¹ represents propargyl and t-butyl radicals.
- 8. Compound of Claim 2, wherein R⁴ represents phenyl and substituted phenyl radicals and wherein R³ represents n-pentyl, n-hexyl, n-propyl, i-butyl, cyclohexyl, neo-pentyl, i-amyl, and n-butyl radicals.
- 9. Compound of Claim 2 wherein R³ and R⁴ independently represent alkyl radicals having from 2 to 5 carbon atoms, cycloalkylalkyl radicals, aralkyl radicals, heterocycloalkylalkyl radicals or heteroaralkyl radicals.
- 10. Compound of Claim 2 wherein R³ represents isobutyl, n-propyl, n-butyl, isoamyl, cyclohexyl, cyclohexylmethyl radicals and R⁴ represents phenyl and substituted phenyl radicals.
- 11. Compound of Claim 10 wherein R³ is i-amyl or i-butyl and R⁴ is phenyl or substituted phenyl selected from para-chlorophenyl, para-fluorophenyl, para-nitrophenyl, para-aminophenyl, and para-methoxyphenyl.
- 12. Compound of Claim 2 wherein R⁴ represents heteroaryl radicals.
- 13. Compound of Claim 2 wherein R³ is a p-fluorobenzyl radical and R⁴ is a phenyl radical or substituted phenyl selected from para-chlorophenyl, para-fluorophenyl, para-nitrophenyl, para-aminophenyl, and para-methoxyphenyl.
- 14. Compound of Claim 2 wherein R³ is a 4-pyridylmethyl radical or its N-oxide and R⁴ is a phenyl radical or substituted phenyl selected from para-chlorophenyl, para-fluorophenyl, para-nitrophenyl, para-aminophenyl, and para-methoxyphenyl.
- 15. Compound of Claim 2 wherein R⁴ represents an alkyl radical having from 1 to 6 carbon atoms or a 5 or 6-membered heterocyclcyl radical, optionally substituted with an alkyl radical having from 1 to 3 carbon atoms.
- 16. Compound of Claim 1 wherein R^{1'} and R^{1''} are both hydrogen and R¹ represents -CH₂SO₂NH₂, CO₂NH₂, C02CH₃,

alkyl and cycloalkyl radicals and amino acid side chains selected from asparagine, S-methyl cysteine and the sulfone and sulfoxide derivatives thereof, histidine, norleucine, glutamine, glycine, allo-isoleucine, alanine, threonine, isoleucine, leucine, tert-leucine, phenylalanine, ornithine, allo-threonine, serine, aspartic acid, beta-cyano alanine and valine side chains.

- 5 17. Compound of Claim 3 or 4 wherein R¹ represents the amino acid side chain of asparagine and R represents a heteroaroyl radical.
- 10 18. Compound of Claim 2 where R¹ represents a t-butyl or a propargyl radical or an amino acid side chain of valine or isoleucine.
- 15 19. Compound of Claim 18 where R represents an arylalkanoyl, aryloxycarbonyl, alkanoyl, aminocarbonyl, mono-substituted aminoalkanoyl, or disubstituted aminoalkanoyl, or mono- or dialkylaminocarbonyl radical.
- 20 20. Compound of Claim 18, where R represents acetyl, N,N-dimethylaminoacetyl, N-methylaminoacetyl or N-benzyl-N-methylaminoacetyl.
- 25 21. Compound of Claim 1 where R¹ is a methyl radical.
22. Compound of Claim 21 where R represents an alkanoyl, arylalkanoyl, aryloxyalkanoyl or arylalkyloxycarbonyl radical.
- 26 23. Compound of Claim 21 where R represents a phenoxyacetyl, 2-naphthyoxyacetyl, benzyloxycarbonyl or p-methoxybenzyloxycarbonyl radical.
- 27 24. Compound of Claim 21 wherein R represents an N,N-dialkylaminocarbonyl radical.
- 28 25. Compound of Claim 21 wherein R represents an aminocarbonyl or an alkylaminocarbonyl radical.
- 30 26. Compound of Claim 21 where R represents an N-methylaminocarbonyl radical.
- 35 27. Compound according to Claim 1 wherein t = 1, R^{1'} and R^{1''} are hydrogen, x is 2; Y is O, R⁶ is hydrogen and wherein R, R², R³, R⁴ are as defined in Claim 1 and R¹ is as in Claim 1 except O-alkylserine and R' is as in Claim 1 except R" SO₂.
- 36 28. Compound of Claim 27 wherein R¹ represents alkyl radicals having from 1 to 4 carbon atoms and alkynyl radicals having from 3 to 8 carbon atoms.
- 40 29. Compound of Claim 27 wherein R¹ represents methyl, ethyl, isopropyl, propargyl and t-butyl radicals.
30. Compound of Claim 27, wherein R' is hydrogen and R is



acetyl, phenoxyacetyl, 2-naphthyoxy-carbonyl, benzyloxycarbonyl or p-methoxybenzyloxycarbonyl.

- 50 31. Compound of Claim 27 wherein R' is hydrogen and R is an aralkoxycarbonyl radical or a heteroaralkoxycarbonyl radical.
32. Compound of Claim 27 wherein R and R' are independently selected from methyl and phenethyl radicals.
- 55 33. Compound of Claim 27 wherein R³ represents alkyl radicals having from 2 to 5 carbon atoms and R⁴ represents methyl, phenyl and substituted phenyl radicals.
34. Compound of Claim 27 wherein R³ represents isobutyl, n-propyl, n-butyl, isoamyl, cyclohexylmethyl, cyclohexyl,

benzyl, para-fluorobenzyl, para-methoxybenzyl, para-methylbenzyl and 2-naphthylmethyl radicals and R⁴ represents phenyl and substituted phenyl radicals wherein substituents of the substituted phenyl radical are selected from chloro fluoro, nitro, methoxy and amino substituents.

- 5 35. Compound of Claim 27 wherein R³ is cyclohexylmethyl and R⁴ phenyl, or R³ is i-amyl and R⁴ is phenyl, or R³ is i-butyl and R⁴ is phenyl, or R³ is n-butyl and R⁴ is phenyl, or R³ is cyclohexyl and R⁴ is phenyl.
- 36. Compound of Claim 27 wherein R⁴ represents methyl and cyclohexyl radicals.
- 10 37. Compound of Claim 27 wherein R and R' together with the nitrogen to which they are bonded represent pyrrolidinyl, piperidinyl, morpholinyl, and piperazinyl radicals.
- 38. Compound of Claim 27 wherein R³ represents heteroaralkyl radicals and R⁴ is methyl or phenyl.
- 15 39. Compound according to Claim 1 wherein t = 1, x = 2, Y is O, R⁶ is hydrogen and wherein R, R¹, R¹", R², R⁴ are as defined in Claim 1 and wherein R³ is as in Claim 1 except hydrogen and R¹ is as in Claim 1 except O-alkylserine and wherein R' is as in Claim 1 except R" SO₂.
- 20 40. Compound of Claim 39 wherein R' represents hydrogen and R represents aralkoxycarbonyl and heteroaroyl radicals.
- 41. Compound of Claim 39 wherein R' is hydrogen and R represents carbobenzoxy, 2-benzofurancarbonyl, and 2-quinolinylcarbonyl radicals.
- 25 42. Compound of Claim 39 wherein R¹, R¹' and R¹" independently represent hydrogen and alkyl radicals having from 1 to about 4 carbon atoms, alkenyl, alkynyl, aralkyl radicals and radicals selected from -CH₂SO₂NH₂, -CO₂CH₃, -CONHCH₃, -CON(CH₃)₂, -CH₂C(O)NHCH₃, -CH₂C(O)N(CH₃)₂, -CONH₂, -C(CH₃)₂(SCH₃), -C(CH₃)₂(S[O])CH₃ and -C(CH₃)₂(S[O]CH₃).
- 30 43. Compound of Claim 39 wherein R¹, R¹' and R¹" independently represent hydrogen, methyl, ethyl, benzyl, phenyl-propyl, propargyl, hydroxyl and radicals selected from -C(O)OCH₃, -C(O)NH₂, -C(O)OH.
- 44. Compound of Claim 39 wherein R¹ and R¹' are both hydrogen and R¹" is C(O)NH₂.
- 35 45. Compound of Claim 39 wherein R¹ and R¹' are both hydrogen and R¹" is methyl.
- 46. Compound of Claim 39 wherein R¹' is hydrogen and R¹ and R¹" together with the carbon atoms to which they are attached form a three to six-membered cycloalkyl radical.
- 40 47. Compound of Claim 44 wherein R is carbobenzoxy, 2-quinolinylcarbonyl and 2-benzofuran carbonyl radicals.
- 48. Compound of Claim 39 wherein R³ represents alkyl radicals having from 2 to 5 carbon atoms.
- 45 49. Compound of Claim 39 wherein R³ independently represent n-propyl, i-butyl, cyclohexyl, cyclohexylmethyl, i-amyl, and n-butyl radicals and R⁴ represents phenyl and substituted phenyl radicals.
- 50 50. Compound of Claim 39 wherein R³ and R⁴ independently represent alkyl radicals having from 2 to 5 carbon atoms, cycloalkylalkyl radicals, aryl radicals, heteroaryl radicals, aralkyl radicals, heterocycloalkylalkyl radicals and heteroaralkyl radicals.
- 51. Compound of Claim -39 wherein R³ represents benzyl, para-fluorobenzyl, para-methoxybenzyl, para-methylbenzyl, and 2-naphthylmethyl radicals and R⁴ represents phenyl and substituted phenyl radicals wherein substituents of the substituted phenyl radical are selected from chloro fluoro, nitro, methoxy and amino substituents.
- 55 52. Compound of Claim 2, 27 or 39 wherein R² represents alkyl, cycloalkylalkyl radicals, which radicals are optionally substituted with halogen radicals and radicals represented by the formula -OR⁹ and -SR⁹ wherein R⁹ represents hydrogen and alkyl radicals.

53. Compound of Claim 2, 27 or 39 wherein R² represents CH₃SCH₂CH₂-, iso-butyl, n-butyl, benzyl, 2-naphthylmethyl and cyclohexylmethyl radicals.

54. Compound of Claim 2, 27 or 39 wherein R³ and R⁴ independently represent alkyl, haloalkyl, alkenyl, alkoxyalkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl, aryl, aralkyl and heteroaralkyl radicals.

55. Compound of Claim 2, 27 or 39 wherein R³ represents alkyl and alkenyl radicals and R⁴ represents aryl radicals.

10 56. A pharmaceutical composition comprising a compound according to any of Claims 1, 2, 27 or 39 and a pharmaceutically acceptable carrier.

57. Use of a composition of Claim 56 for preparing a medicament for inhibiting a retroviral protease.

15 58. Use according to Claim 57 wherein the retroviral protease is HIV protease.

59. Use of a composition of Claim 56 for preparing a medicament for treating a retroviral infection.

60. Use according to Claim 59 wherein the retroviral infection is an HIV infection.

20 61. Use of a composition of Claim .56 for preparing a medicament for treating AIDS.

62. A compound of Claim 1 which is:

25 Phenylmethyl[2R-hydroxy-3-[(3-methylbutyl)(methylsulfonyl)amino]-1S-(phenylmethyl)propyl]carbamate;

Phenylmethyl[2R-hydroxy-3-[(3-methylbutyl)(phenylsulfonyl)amino]-1S-(phenylmethyl)propyl]carbamate;

30 N1-[2R-hydroxy-3-[(3-methylbutyl)(methylsulfonyl)amino]-1S-(phenylmethyl)propyl]-2S-[(2-quinolinylcarbo-nyl)amino]butanediamide;

N1-[2R-hydroxy-3-[(3-methylbutyl)(methylsulfonyl)amino]-1S-(phenylmethyl)propyl]-2S-[(phenylmethoxy-carbonyl)amino]butanediamide;

35 N1-[2R-hydroxy-3[(3-methylbutyl)(ptenylsulfonyl)amino]-1S-(phenylmethyl)propyl]-2S-[(2-quinolinylcarbo-nyl)-amino]butanediamide;

N1-[2R-hydroxy-3[(3-methylbutyl)(phenylsulfonyl)-amino]-1S-(phenylmethyl)propyl]-2S-[(phenylmethoxy-carbonyl)amino]butanediamide;

40 2S-[[dimethylamino]acetyl]amino]-N-[2R-hydroxy-3-[(3-methyl- butyl)(phenylsulfonyl)amino]-1S-(phenylme-thyl)propyl]-3,3-dimethylbutaneamide;

45 2S-[(methylamino)acetyl]amino]-N-[2R-hydroxy-3-[(3-methyl- butyl)(phenylsulfonyl)amino]-1S-(phenylme-thyl)propyl]-3,3-dimethylbutaneamide; or

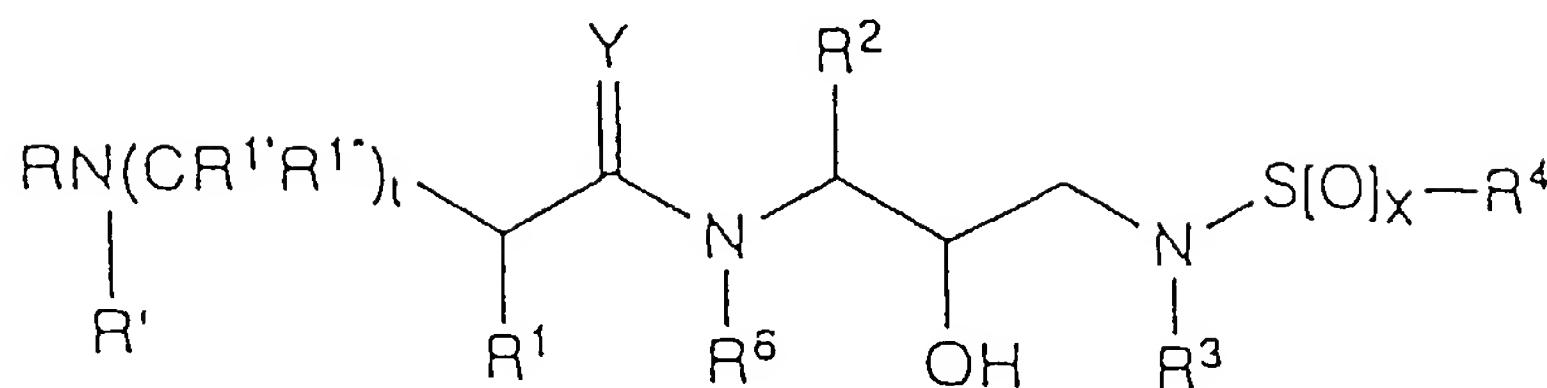
N1-[2R-hydroxy-3-[(3-methylbutyl)(phenyl-sulfonyl)amino]-N4-methyl-1S-(phenylmethyl)propyl]-2S-[(2-quin-olinylcarbonyl)amino]butanediamide; or

50 Carbamic acid, [3-[[2-hydroxy-3-[(3-methylbutyl)(phenylsufonyl)amino]-1-(phenylmethyl)propyl]amino]-2-me-thyl-3-oxopropyl]-, (4-methoxyphenyl)methyl ester, [1S-[1R*(S*),2S*]]-.

Patentansprüche

55

1. Verbindung mit der Formel



10 oder ein pharmazeutisch unbedenkliches Salz, Prodrug oder Ester davon, worin

R Wasserstoff, Alkoxy carbonyl-, Aralkoxy carbonyl-, Alkyl carbonyl-, Cycloalkyl carbonyl-, Cycloalkylalkoxy carbonyl-, Cycloalkyl alkanoyl-, Alkanoyl-, Aralkanoyl-, Aroyl-, Aryloxy carbonyl-, Aryloxy carbonylalkyl-, Aryloxy alkanoyl-, Heterocyclyl carbonyl-, Heterocyclyl oxy carbonyl-, Heterocyclyl alkanoyl-, Heterocyclyl alkoxy carbonyl-, Heteroaralkanoyl-, Heteroaralkoxy carbonyl-, Heteroaryl oxy carbonyl-, Heteroaryl-, Alkyl-, Alkenyl-, Alkinyl-, Cycloalkyl-, Aryl-, Aralkyl-, Aryloxy alkyl-, Heteroaryloxy alkyl-, Hydroxy alkyl-, Aminocarbonyl-, Amino alkanoyl- und mono- und disubstituierte Aminocarbonyl- und mono- und disubstituierte Amino alkanoylreste, worin die Substituenten ausgewählt sind aus Alkyl-, Aryl-, Aralkyl-, Cycloalkyl-, Cycloalkylalkyl-, Heteroaryl-, Heteroaralkyl-, Heterocycloalkyl-, Heterocycloalkylalkylresten oder, wo die Aminocarbonyl- und Amino alkanoylreste disubstituiert sind, diese Substituenten zusammen mit dem Stickstoffatom, an das sie gebunden sind, einen Heterocycloalkyl- oder Heteroarylrest bilden, bedeutet;

R' Wasserstoff oder Reste, wie sie für R³ definiert sind, oder R"SO₂⁻, worin R" Reste darstellt, wie sie für R³ definiert sind, bedeutet; oder R und R' zusammen mit dem Stickstoff, an den sie gebunden sind, einen Heterocycloalkyl- und Heteroarylrest darstellen;

25 R¹ Wasserstoff, -CH₂SO₂NH₂, -CH₂CO₂CH₃, -CO₂CH₃, -CONH₂, -CH₂C(O)NHCH₃, -C(CH₃)₂(SH), -C(CH₃)₂(SCH₃), -C(CH₃)₂(S[O]CH₃), C(CH₃)₂(S[O]₂CH₃), Alkyl-, Halogenalkyl-, Alkenyl-, Alkinyl- und Cycloalkylreste und Aminosäureseitenketten ausgewählt aus Asparagin-, S-Methylcystein- und Sulfoxid(SO)- und Sulfon (SO₂)-Derivaten davon, Isoleucin-, Alloisoleucin-, Alanin-, Leucin-, tert-Leucin-, Phenylalanin-, Ornithin-, Histidin-, Norleucin-, Glutamin-, Threonin-, Glycin-, Allothreonin-, Serin-, O-Alkylserin-, Asparaginsäure-, beta-Cyanoalanin- und Valinseitenketten bedeutet;

30 R^{1'} und R^{1''} unabhängig Wasserstoff und Reste, wie sie für R¹ definiert sind, bedeuten, oder eines von R^{1'} und R^{1''} zusammen mit R¹ und den Kohlenstoffatomen, an die R¹, R^{1'} und R^{1''} gebunden sind, einen Cycloalkylrest darstellt;

35 R² Alkyl-, Aryl-, Cycloalkyl-, Cycloalkylalkyl- und Aralkylreste, welche Reste gegebenenfalls substituiert sind mit einer Gruppe ausgewählt aus Alkyl- und Halogenresten, -NO₂, -C≡N, CF₃, -OR⁹, -SR⁹, worin R⁹ Wasserstoff und Alkylreste darstellt, bedeutet;

40 R³ Wasserstoff, Alkyl-, Halogenalkyl-, Alkenyl-, Alkinyl-, Hydroxy alkyl-, Alkoxy alkyl-, Cycloalkyl-, Cycloalkylalkyl-, Heterocycloalkyl-, Heteroaryl-, Heterocycloalkylalkyl-, Aryl-, Aralkyl-, Heteroaralkyl-, Amino alkyl- und mono- und disubstituierte Amino alkylreste, worin die Substituenten ausgewählt sind aus Alkyl-, Aryl-, Aralkyl-, Cycloalkyl-, Cycloalkylalkyl-, Heteroaryl-, Heteroaralkyl-, Heterocycloalkyl- und Heterocycloalkylalkylresten, oder, im Falle eines disubstituierten Amino alkylrestes, die Substituenten zusammen mit dem Stickstoffatom, an das sie gebunden sind, einen Heterocycloalkyl- oder einen Heteroarylrest bilden, bedeutet;

45 R⁴ Reste darstellt, wie sie durch R³ definiert sind, mit Ausnahme von Wasserstoff;

R⁶ Wasserstoff und Alkylreste darstellt;

x für 0, 1 oder 2 steht;

t für 0 oder 1 steht; und

Y für O, S und NR¹⁵ steht, wobei R¹⁵ Wasserstoff und Reste, wie sie für R³ definiert sind, darstellt.

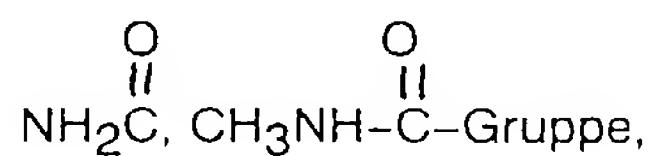
- 50 2. Verbindung nach Anspruch 1, worin t 0 ist, Y O ist, x 2 ist, R⁶ = Wasserstoff und R' wie im Anspruch 1, außer R"SO₂, mit R¹ wie im Anspruch 1 definiert, außer daß O-Alkylserin durch O-Methylserin ersetzt ist, mit R³ wie im Anspruch 1, außer Wasserstoff, mit R, R² und R⁴ wie im Anspruch 1 definiert.
3. Verbindung nach Anspruch 2, worin R für Aralkoxy carbonyl- und Heteroaroylreste steht.
- 55 4. Verbindung nach Anspruch 2, worin R für Carbobenzoxy-, 2-Benzofurancarbonyl- und 2-Chinolinylcarbonylreste steht.
5. Verbindung nach Anspruch 2, worin R¹ Alkyl-, Alkinyl- und Alkenylreste und Aminosäureseitenketten ausgewählt

aus der Gruppe bestehend aus Asparagin, Valin, Threonin, Allothreonin, Isoleucin, S-Methylcystein und Sulfon- und Sulfoxidderivaten davon, Alanin und Alloisoleucin darstellt.

6. Verbindung nach Anspruch 2, worin R¹ Methyl-, Propargyl-, t-Butyl-, Isopropyl- und sec-Butylreste und Aminosäureseitenketten ausgewählt aus der Gruppe bestehend aus Asparagin-, Valin-, S-Methylcystein-, Alloisoleucin-, Isoleucin-, Threonin-, Serin-, Asparaginsäure-, beta-Cyanoalanin- und Allothreoninseitenketten darstellt.
7. Verbindung nach Anspruch 2, worin R¹ Propargyl- und t-Butylreste darstellt.
8. Verbindung nach Anspruch 2, worin R⁴ Phenyl- und substituierte Phenylreste darstellt und worin R³ n-Pentyl-, n-Hexyl-, n-Propyl-, i-Butyl-, Cyclohexyl-, Neopentyl-, i-Amyl- und n-Butylreste darstellt.
9. Verbindung nach Anspruch 2, worin R³ und R⁴ unabhängig Alkylreste mit 2 bis 5 Kohlenstoffatomen, Cycloalkylreste, Aralkylreste, Heterocycloalkylalkylreste oder Heteroaralkylreste darstellen.
10. Verbindung nach Anspruch 2, worin R³ Isobutyl-, n-Propyl-, n-Butyl-, Isoamyl-, Cyclohexyl-, Cyclohexylmethylreste darstellt und R⁴ Phenyl- und substituierte Phenylreste darstellt.
11. Verbindung nach Anspruch 10, worin R³ i-Amyl oder i-Butyl ist und R⁴ Phenyl oder substituiertes Phenyl ausgewählt aus p-Chlorphenyl, p-Fluorphenyl, p-Nitrophenyl, p-Aminophenyl und p-Methoxyphenyl darstellt.
12. Verbindung nach Anspruch 2, worin R⁴ Heteroarylreste darstellt.
13. Verbindung nach Anspruch 2, worin R³ ein p-Fluorbenzylrest ist und R⁴ ein Phenylrest oder substituierter Phenylrest ausgewählt aus p-Chlorphenyl, p-Fluorphenyl, p-Nitrophenyl, p-Aminophenyl und p-Methoxyphenyl ist.
14. Verbindung nach Anspruch 2, worin R³ ein 4-Pyridylmethylrest oder dessen N-Oxid ist und R⁴ ein Phenylrest oder ein substituierter Phenylrest ausgewählt aus p-Chlorphenyl, p-Fluorphenyl, p-Nitrophenyl, p-Aminophenyl und p-Methoxyphenyl ist.
15. Verbindung nach Anspruch 2, worin R⁴ einen Alkylrest mit 1 bis 6 Kohlenstoffatomen oder einen 5- oder 6-gliedrigen Heterocyclrest, der gegebenenfalls mit einem Alkylrest mit 1 bis 3 Kohlenstoffatomen substituiert ist, darstellt.
16. Verbindung nach Anspruch 1, worin R^{1'} und R^{1''} beide Wasserstoff sind und R¹ für -CH₂SO₂NH₂, CO₂NH₂, CO₂CH₃, Alkyl- und Cycloalkylreste und Aminosäureseitenketten ausgewählt aus Asparagin-, S-Methylcystein- und den Sulfon- und Sulfoxidderivaten davon, Histidin-, Norleucin-, Glutamin-, Glycin-, Alloisoleucin-, Alanin-, Threonin-, Isoleucin-, Leucin-, tert-Leucin-, Phenylalanin-, Ornithin-, Allothreonin-, Serin-, Asparaginsäure-, beta-Cyanoalanin- und Valinseitenketten darstellt.
17. Verbindung nach Anspruch 3 oder 4, worin R¹ die Aminosäureseitenkette von Asparagin und R einen Heteroaroylrest darstellt.
18. Verbindung nach Anspruch 2, worin R¹ einen t-Butyl- oder einen Propargylrest oder eine Aminosäureseitenkette von Valin oder Isoleucin darstellt.
19. Verbindung nach Anspruch 18, worin R einen Arylalkanoyl-, Aryloxycarbonyl-, Alkanoyl-, Aminocarbonyl-, mono-substituierten Aminoalkanoyl- oder disubstituierten Aminoalkanoyl- oder Mono- oder Dialkylaminocarbonylrest darstellt.
20. Verbindung nach Anspruch 18, worin R Acetyl, N,N-Dimethylaminoacetyl, N-Methylaminoacetyl oder N-Benzyl-N-methylaminoacetyl darstellt.
21. Verbindung nach Anspruch 1, worin R¹ einen Methylrest darstellt.
22. Verbindung nach Anspruch 21, worin R einen Alkanoyl-, Arylalkanoyl-, Aryloxyalkanoyl- oder Arylalkyloxycarbonylrest darstellt.
23. Verbindung nach Anspruch 21, worin R einen Phenoxyacetyl-, 2-Naphthyoxyacetyl-, Benzyloxycarbonyl- oder p-

Methoxybenzyloxycarbonylrest darstellt.

24. Verbindung nach Anspruch 21, worin R einen N,N-Dialkylaminocarbonylrest darstellt.
- 5 25. Verbindung nach Anspruch 21, worin R einen Aminocarbonyl- oder einen Alkylaminocarbonylrest darstellt.
26. Verbindung nach Anspruch 21, worin R einen N-Methylaminocarbonylrest darstellt.
- 10 27. Verbindung nach Anspruch 1, worin t = 1, R^{1'} und R^{1''} Wasserstoff sind, x 2 ist; Y O ist, R⁶ Wasserstoff ist und worin R, R², R³, R⁴ wie im Anspruch 1 definiert sind und R¹ wie im Anspruch 1 ist, außer O-Alkylserin, und R' wie im Anspruch 1 ist, außer R"SO₂.
- 15 28. Verbindung nach Anspruch 27, worin R¹ Alkylreste mit 1 bis 4 Kohlenstoffatomen und Alkinylreste mit 3 bis 8 Kohlenstoffatomen darstellt.
29. Verbindung nach Anspruch 27, worin R¹ Methyl-, Ethyl-, Isopropyl-, Propargyl- und t-Butylreste darstellt.
30. Verbindung nach Anspruch 27, worin R' Wasserstoff ist und R



25 Acetyl, Phenoxyacetyl, 2-Naphthyloxycarbonyl, Benzyloxycarbonyl oder p-Methoxybenzyloxycarbonyl ist.

31. Verbindung nach Anspruch 27, worin R' Wasserstoff darstellt und R ein Aralkoxycarbonylrest oder ein Heteroaralkoxycarbonylrest ist.
32. Verbindung nach Anspruch 27, worin R und R' unabhängig aus Methyl- und Phenethylresten ausgewählt sind.
- 30 33. Verbindung nach Anspruch 27, worin R³ Alkylreste mit 2 bis 5 Kohlenstoffatomen und R⁴ Methyl-, Phenyl- und substituierte Phenylreste darstellt.
34. Verbindung nach Anspruch 27, worin R³ Isobutyl-, n-Propyl-, n-Butyl-, Isoamyl-, Cyclohexylmethyl-, Cyclohexyl-, Benzyl-, p-Fluorbenzyl-, p-Methoxybenzyl-, p-Methylbenzyl- und 2-Naphthylmethylreste darstellt und R⁴ Phenyl- und substituierte Phenylreste darstellt, worin die Substituenten des substituierten Phenylrestes aus Chlor-, Fluor-, Nitro-, Methoxy- und Aminosubstituenten ausgewählt sind.
- 35 35. Verbindung nach Anspruch 27, worin R³ Cyclohexylmethyl und R⁴ Phenyl ist, oder R³ i-Amyl und R⁴ Phenyl ist, oder R³ i-Butyl und R⁴ Phenyl ist, oder R³ n-Butyl und R⁴ Phenyl ist, oder R³ Cyclohexyl und R⁴ Phenyl ist.
36. Verbindung nach Anspruch 27, worin R⁴ Methyl- oder Cyclohexylreste darstellt.
37. Verbindung nach Anspruch 27, worin R und R' zusammen mit dem Stickstoff, an den sie gebunden sind, Pyrrolidinyl-, Piperidinyl-, Morpholinyl- und Piperazinylreste darstellen.
- 45 38. Verbindung nach Anspruch 27, worin R³ Heteroaralkylreste darstellt und R⁴ Methyl oder Phenyl ist.
39. Verbindung nach Anspruch 1, worin t = 1, x = 2, Y für O steht, R⁶ Wasserstoff ist und worin R, R^{1'}, R^{1''}, R², R⁴ wie im Anspruch 1 definiert sind und worin R³ wie im Anspruch 1 ist, außer Wasserstoff, und R¹ wie im Anspruch 1 ist, außer O-Alkylserin, und worin R' wie im Anspruch 1 ist, außer R"SO₂.
- 50 40. Verbindung nach Anspruch 39, worin R' Wasserstoff darstellt und R Aralkoxycarbonyl- und Heteroaroylreste darstellt.
- 55 41. Verbindung nach Anspruch 39, worin R' Wasserstoff ist und R für Carbobenzoxy-, 2-Benzofurancarbonyl- und 2-Chinolinylcarbonylreste steht.

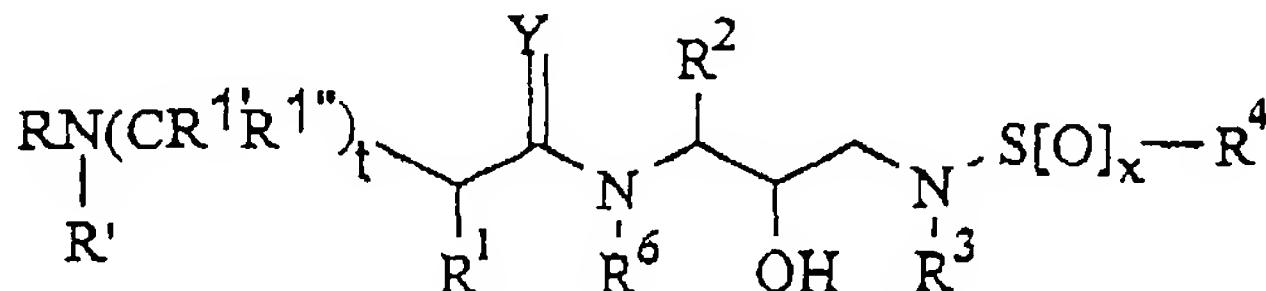
42. Verbindung nach Anspruch 39, worin R¹, R^{1'} und R^{1''} unabhängig Wasserstoff und Alkylreste mit 1 bis etwa 4 Kohlenstoffatomen, Alkenyl-, Alkinyl-, Aralkylreste und Reste ausgewählt aus -CH₂SO₂NH₂, -CO₂CH₃, -CONHCH₃, -CON(CH₃)₂, -CH₂C(O)NHCH₃, -CH₂C(O)N(CH₃)₂, -CONH₂, -C(CH₃)₂(SCH₃), -C(CH₃)₂(S[O]CH₃) und -C(CH₃)₂(S[O]CH₃) darstellen.
- 5
43. Verbindung nach Anspruch 39, worin R¹, R^{1'} und R^{1''} unabhängig Wasserstoff, Methyl, Ethyl, Benzyl, Phenylpropyl, Propargyl, Hydroxyl und Reste ausgewählt aus -C(O)OCH₃, -C(O)NH₂, -C(O)OH darstellen.
- 10
44. Verbindung nach Anspruch 39, worin R¹ und R^{1'} beide Wasserstoff sind und R^{1''} C(O)NH₂ ist.
45. Verbindung nach Anspruch 39, worin R¹ und R^{1'} beide Wasserstoff sind und R^{1''} Methyl ist.
- 15
46. Verbindung nach Anspruch 39, worin R^{1'} Wasserstoff ist und R¹ und R^{1''} zusammen mit den Kohlenstoffatomen, an die sie gebunden sind, einen 3- bis 6-gliedrigen Cycloalkylrest bilden.
47. Verbindung nach Anspruch 44, worin R Carbobenzoxy-, 2-Chinolinylcarbonyl- und 2-Benzofurancarbonylreste darstellt.
- 20
48. Verbindung nach Anspruch 39, worin R³ Alkylreste mit 2 bis 5 Kohlenstoffatomen darstellt.
49. Verbindung nach Anspruch 39, worin R³ unabhängig n-Propyl-, i-Butyl-, Cyclohexyl-, Cyclohexylmethyl-, i-Amyl- und n-Butylreste darstellt und R⁴ Phenyl- und substituierte Phenylreste darstellt.
50. Verbindung nach Anspruch 39, worin R³ und R⁴ unabhängig Alkylreste mit 2 bis 5 Kohlenstoffatomen, Cycloalkylalkylreste, Arylreste, Heteroarylreste, Aralkylreste, Heterocycloalkylalkylreste und Heteroaralkylreste darstellen.
- 25
51. Verbindung nach Anspruch 39, worin R³ Benzyl-, p-Fluorbenzyl-, p-Methoxybenzyl-, p-Methylbenzyl- und 2-Naphthylmethylreste darstellt und R⁴ Phenyl- und substituierte Phenylreste darstellt, wobei die Substituenten der substituierten Phenylreste ausgewählt sind aus Chlor-, Fluor-, Nitro-, Methoxy- und Aminosubstituenten.
- 30
52. Verbindung nach Anspruch 2, 27 oder 39, worin R² Alkyl-, Cycloalkylalkylreste darstellt, welche Reste gegebenenfalls substituiert sind mit Halogenresten und Resten, die dargestellt werden durch die Formel -OR⁹ und -SR⁹, worin R⁹ Wasserstoff und Alkylreste darstellt.
- 35
53. Verbindung nach Anspruch 2, 27 oder 39, worin R² CH₃SCH₂CH₂- Isobutyl, n-Butyl-, Benzyl-, 2-Naphthylmethyl- und Cyclohexylmethylreste darstellt.
54. Verbindung nach Anspruch 2, 27 oder 39, worin R³ und R⁴ unabhängig Alkyl-, Halogenalkyl-, Alkenyl-, Alkoxyalkyl-, Cycloalkyl-, Cycloalkylalkyl-, Heterocycloalkyl-, Heterocycloalkylalkyl-, Heteroaryl-, Aryl-, Aralkyl- und Heteroaralkylreste darstellen.
- 40
55. Verbindung nach Anspruch 2, 27 oder 39, worin R³ Alkyl- und Alkenylreste darstellt und R⁴ Arylreste darstellt.
56. Pharmazeutische Zusammensetzung, umfassend eine Verbindung nach irgendeinem der Ansprüche 1, 2, 27 oder 39 und einen pharmazeutisch unbedenklichen Träger.
- 45
57. Verwendung einer Zusammensetzung nach Anspruch 56 zur Herstellung eines Medikaments zur Hemmung einer retroviralen Protease.
58. Verwendung nach Anspruch 57, worin die retrovirale Protease HIV-Protease ist.
- 50
59. Verwendung einer Zusammensetzung nach Anspruch 56 zur Herstellung eines Medikaments zur Behandlung einer retroviralen Infektion.
60. Verwendung nach Anspruch 59, worin die retrovirale Infektion eine HIV-Infektion ist.
- 55
61. Verwendung einer Zusammensetzung nach Anspruch 56 zur Herstellung eines Medikaments zur Behandlung von AIDS.

62. Verbindung nach Anspruch 1, welche ist:

Phenylmethyl[2R-hydroxy-3-[(3-methylbutyl)(methylsulfonyl)amino]-1S-(phenylmethyl)propyl]carbamat;
 Phenylmethyl[2R-hydroxy-3-[(3-methylbutyl)(phenylsulfonyl)amino]-1S-(phenylmethyl)propyl]carbamat;
 5 N1-[2R-Hydroxy-3-[(3-methylbutyl)(methylsulfonyl)amino]-1S-(phenylmethyl)propyl]-2S-[(2-chinolinylcarbo-
 nyl)amino]butandiamid;
 N1-[2R-Hydroxy-3-[(3-methylbutyl)(methylsulfonyl)amino]-1S-(phenylmethyl)propyl]-2S-[(phenylmethoxy-
 carbonyl)amino]butandiamid;
 10 N1-[2R-Hydroxy-3-[(3-methylbutyl)(phenylsulfonyl)amino]-1S-(phenylmethyl)propyl]-2S-[(2-chinolinylcarbo-
 nyl)amino]butandiamid;
 N1-[2R-Hydroxy-3-[(3-methylbutyl)(phenylsulfonyl)amino]-1S-(phenylmethyl)propyl]-2S-[(phenylmethoxy-
 carbonyl)amino]butandiamid;
 15 2S-[(Dimethylamino)acetyl]amino]-N-[2R-hydroxy-3-[(3-methylbutyl)(phenylsulfonyl)amino]-1S-(phenylme-
 thyl)propyl]-3,3-dimethylbutanamid; oder
 N1-[2R-Hydroxy-3-[(3-methylbutyl)(phenylsulfonyl)amino]-N4-methyl-1S-(phenylmethyl)propyl]-2S-[(2-chi-
 nolinylcarbonyl)amino]butandiamid; oder
 20 Carbamidsäure, [3-[[2-Hydroxy-3-[(3-methylbutyl)(phenylsulfonyl)amino]-1-(phenylmethyl)propyl]amino]-
 2-methyl-3-oxopropyl]-, (4-Methoxyphenyl)methylester, [1S-[1R*(S*),2S*]]-.

Revendications

25 1. Composé représenté par la formule:



ou un de ses sels pharmaceutiquement acceptables, une de ses prodrugs ou un de ses esters, dans laquelle :

35 R représente un hydrogène, des radicaux alcoxycarbonyle, arylalcoxycarbonyle, alkylcarbonyle, cycloalkyl-
 carbonyle, cycloalkylalcoxycarbonyle, cycloalkylalcanoyle, alcanolyte, arylalcanoyle, aroyle, aryloxycarbony-
 le, aryloxycarbonylalkyle, aryloxyalcanoyle, hétérocyclcarbonyle, hétérocyclloxycarbonyle, hétérocyclal-
 canoyle, hétérocyclalcoxycarbonyle, hétéroarylalcanoyle, hétéroarylalcoxycarbonyle, hétéroaryloxykarbo-
 nyle, hétéroaroyle, alkyle, alcényle, alcynyle, cycloalkyle, aryle, arylalkyle, aryloxyalkyle, hétéroaryloxyalkyle,
 40 hydroxyalkyle, aminocarbonyle, aminoalcanoyle et aminocarbonyle mono- et disubstitué et aminoalcanoyle
 mono- et disubstitué, les substituants étant choisis parmi les radicaux alkyle, aryle, arylalkyle, cycloalkyle,
 cycloalkylalkyle, hétéroaryle, hétéroarylalkyle, hétérocycloalkyle, hétérocycloalkylalkyle, ou, quand lesdits ra-
 dicaux aminocarbonyle et aminoalcanoyle sont disubstitués, lesdits substituants formant, avec l'atome d'azote
 45 auquel ils sont rattachés, un radical hétérocycloalkyle ou hétéroaryle ;

R' représente un hydrogène et des radicaux tels que définis pour R³, ou R"SO₂⁻ dans laquelle R" représente
 les radicaux tels que définis pour R³ ; ou R et R' représentent ensemble, avec l'azote auquel ils sont fixés, un
 radical hétérocycloalkyle et hétéroaryle ;

50 R¹ représente un hydrogène, des radicaux -CH₂SO₂NH₂, -CH₂CO₂CH₃, -CO₂CH₃, -CONH₂, -CH₂C(O)
 NHCH₃, -C(CH₃)₂(SH), -C(CH₃)₂(SCH₃), -C(CH₃)₂(S[O]CH₃), -C(CH₃)₂(S[O]₂CH₃), alkyle, halogénoalkyle,
 alcényle, alcynyle, et cycloalkyle et des chaînes latérales aminoacides choisies parmi les chaînes latérales
 de l'asparagine, de la S-méthylcystéine et de ses dérivés sulfoxyde (SO) et sulfone (SO₂), de l'isoleucine, de
 l'alioisoleucine, de lalanine, de la leucine, de la tert-leucine, de la phénylalanine, de l'ornithine, de lhistidine,
 de la norleucine, de la glutamine, de la thréonine, de la glycine, de lallothréonine, de la sérine, de la O-
 55 alkylsérine, de l'acide aspartique, de la béta-cyanoalanine et de la valine ;

R¹' et R¹'' représentent chacun de façon indépendante un hydrogène et les radicaux tels que définis pour R¹,
 ou un des R¹ et R¹'', avec R¹ et les atomes de carbone auxquels R¹, R¹' et R¹'' sont rattachés, représentent
 un radical cycloalkyle ;

R² représente des radicaux alkyle, aryle, cycloalkyle, cycloalkylalkyle et arylalkyle, radicaux éventuellement substitués par un groupe choisi parmi les radicaux alkyle et halogène, -NO₂, -C≡N, CF₃, -OR⁹, -SR⁹, où R⁹ représente l'hydrogène et des radicaux alkyle ;

R³ représente l'hydrogène, des radicaux alkyle, halogénoalkyle, alcényle, alcynyle, hydroxyalkyle, alcoxyalkyle, cycloalkyle, cycloalkylalkyle, hétérocycloalkyle, hétéroaryle, hétérocycloalkylalkyle, aryle, arylalkyle, hétéroarylalkyle, aminoalkyle et aminoalkyle mono- et disubstitués, lesdits substituants étant choisis parmi les radicaux alkyle, aryle, arylalkyle, cycloalkyle, cycloalkylalkyle, hétéroaryle, hétéroarylalkyle, hétérocycloalkyle et hétérocycloalkylalkyle, ou, dans le cas d'un radical aminoalkyle disubstitué, lesdits substituants formant, avec l'atome d'azote auquel ils sont rattachés, un radical hétérocycloalkyle ou un radical hétéroaryle ;

R⁴ représente les radicaux tels que définis pour R³, exception faite de l'hydrogène ;

R⁶ représente un hydrogène et des radicaux alkyle ;

x représente 0, 1 ou 2 ;

t représente 0 ou 1 ; et

Y représente O, S et NR¹⁵, R¹⁵ représentant un hydrogène et des radicaux tels que définis pour R³.

2. Composé selon la revendication 1, dans lequel t est égal à 0, Y représente O, x est égal à 2, R⁶ = un hydrogène et avec R¹ tel que défini dans la revendication 1, R"SO₂ étant exclu, avec R¹ tel que défini dans la revendication 1, à l'exception du fait que la O-alkylsérine est remplacée par la O-méthylsérine, avec R³ tel que défini dans la revendication 1, l'hydrogène étant exclu, avec R, R² et R⁴ tels que définis dans la revendication 1.
3. Composé selon la revendication 2, dans lequel R représente des radicaux arylalcoxycarbonyle et hétéroaroyle.
4. Composé selon la revendication 2, dans lequel R représente des radicaux carbobenzoxy, 2-benzofurancarbonyle et 2-quinoléinylcarbonyle.
5. Composé selon la revendication 2, dans lequel R¹ représente des radicaux alkyle, alcynyle et alcényle et des chaînes latérales d'aminoacides choisis dans le groupe constitué par l'asparagine, la valine, la thréonine, l'allo-thréonine, l'isoleucine, la S-méthylcystéine et ses dérivés sulfone et sulfoxyde, lalanine et l'allo-isoleucine.
6. Composé selon la revendication 2, dans lequel R¹ représente des radicaux méthyle, propargyle, t-butyle, isopropyle et sec-butyle et des chaînes latérales d'aminoacides choisis dans le groupe constitué par l'asparagine, la valine, la S-méthylcystéine, l'allo-isoleucine, l'isoleucine, la thréonine, la sérine, l'acide aspartique, la bêta-cyanalanine et l'allo-thréonine.
7. Composé selon la revendication 2, dans lequel R¹ représente les radicaux propargyle et t-butyle.
8. Composé selon la revendication 2, dans lequel R⁴ représente des radicaux phényle et phényle substitué et dans lequel R³ représente des radicaux n-pentyle, n-hexyle, n-propyle, i-butyle, cyclohexyle, néo-pentyle, i-amyle et n-butyle.
9. Composé selon la revendication 2, dans lequel R³ et R⁴ représentent chacun de façon indépendante des radicaux alkyle ayant 2 à 5 atomes de carbone, des radicaux cycloalkylalkyle, des radicaux arylalkyle, des radicaux hétérocycloalkylalkyle ou des radicaux hétéroarylalkyle.
10. Composé selon la revendication 2, dans lequel R³ représente des radicaux isobutyle, n-propyle, n-butyle, isoamyle, cyclohexyle, cyclohexylméthyle et R⁴ représente des radicaux phényle et phényle substitué.
11. Composé selon la revendication 10, dans lequel R³ est un radical i-amyle ou i-butyle et R⁴ est un radical phényle ou un radical phényle substitué choisi parmi para-chlorophényle, para-fluorophényle, para-nitrophényle, para-aminophényle et para-méthoxyphényle.
12. Composé selon la revendication 2, dans lequel R⁴ représente des radicaux hétéroaryle.
13. Composé selon la revendication 2, dans lequel R³ est un radical p-fluorobenzyle et R⁴ est un radical phényle ou un radical phényle substitué choisi parmi para-chlorophényle, para-fluorophényle, para-nitrophényle, para-amino-phényle et para-méthoxyphényle.
14. Composé selon la revendication 2, dans lequel R³ est un radical 4-pyridylméthyle ou son N-oxyde et R⁴ est un

radical phényle ou un radical phényle substitué choisi parmi para-chlorophényle, para-fluorophényle, para-nitrophényle, para-aminophényle et para-méthoxyphényle.

15. Composé selon la revendication 2, dans lequel R⁴ représente un radical alkyle contenant 1 à 6 atomes de carbone
5 ou un radical hétérocyclique penta- ou hexagonal, éventuellement substitué par un radical alkyle contenant 1 à 3 atomes de carbone.

16. Composé selon la revendication 1, dans lequel R^{1'} et R^{1''} sont tous deux un hydrogène et R¹ représente des
10 radicaux -CH₂SO₂NH₂, -CO₂NH₂, -CO₂CH₃, alkyle et cycloalkyle et des chaînes latérales d'aminoacides choisies
parmi les chaînes latérales de l'asparagine, de la S-méthylcystéine et de ses dérivés sulfone et sulfoxyde, de
l'histidine, de la norleucine, de la glutamine, de la glycine, de l'allo-isoleucine, de lalanine, de la thréonine, de
l'isoleucine, de la leucine, de la tert-leucine, de la phénylalanine, de l'ornithine, de l'allo-thréonine, de la sérine, de
l'acide aspartique, de la béta-cyanoalanine et de la valine.

15. Composé selon la revendication 3 ou 4, dans lequel R¹ représente la chaîne latérale de l'aminoacide asparagine
et R représente un radical hétéroaroyle.

18. Composé selon la revendication 2, dans lequel R¹ représente un radical t-butyle ou propargyle ou la chaîne latérale
20 de l'aminoacide valine ou isoleucine.

19. Composé selon la revendication 18, dans lequel R représente un radical arylalcanoyle, aryloxycarbonyle, alca-
noyle, aminocarbonyle, aminoalcanoyle mono-substitué ou aminoalcanoyle disubstitué ou mono- ou dialkylamino-
nocarbonyle.

25. Composé selon la revendication 18, dans lequel R représente un radical acétyle, N,N-diméthylaminoacétyle, N-
méthylaminoacétyle ou N-benzyl-N-méthylaminoacétyle.

21. Composé selon la revendication 1, dans lequel R¹ représente un radical méthyle.

30. 22. Composé selon la revendication 21, dans lequel R représente un radical alcanoyle, arylalcanoyle, aryloxyalcanoyle
ou arylalkyloxycarbonyle.

23. Composé selon la revendication 21, dans lequel R représente un radical phenoxyacétyle, 2-naphtyloxyacétyle,
benzyloxycarbonyle ou p-méthoxybenzyloxycarbonyle.

35. 24. Composé selon la revendication 21, dans lequel R représente un radical N,N-dialkylaminocarbonyle.

25. Composé selon la revendication 21, dans lequel R représente un radical aminocarbonyle ou alkylaminocarbonyle.

40. 26. Composé selon la revendication 21, dans lequel R représente un radical N-méthylaminocarbonyle.

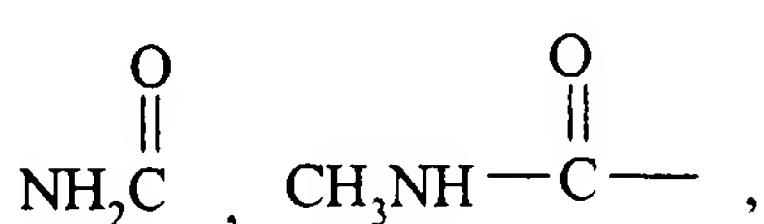
27. Composé selon la revendication 1, dans lequel t est égal à 1, R^{1'} et R^{1''} représentent l'hydrogène, x est égal à 2,
Y représente O, R⁶ est un hydrogène et dans lequel R, R², R³, R⁴ sont tels que définis dans la revendication 1 et
45 R¹ est tel que défini dans la revendication 1, les O-alkylsérines étant exclues et R' est tel que dans la revendication
1, R"SO₂ étant exclu.

28. Composé selon la revendication 27, dans lequel R' représente des radicaux alkyle ayant 1 à 4 atomes de carbone
et des radicaux alcynyle ayant 3 à 8 atomes de carbone.

50. 29. Composé selon la revendication 27, dans lequel R¹ représente des radicaux méthyle, éthyle, isopropyle, propargyle et t-butyle.

30. Composé selon la revendication 27, dans lequel R' est l'hydrogène, et R est un groupe

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acétyle, phénoxyacétyle, 2-naphtyloxycarbonyle, benzyloxycarbonyle ou p-méthoxybenzyloxycarbonyle.

31. Composé selon la revendication 27, dans lequel R' est l'hydrogène et R représente un radical arylalcoxycarbonyle ou un radical hétéroarylalcoxycarbonyle.
32. Composé selon la revendication 27, dans lequel R et R' sont choisis de façon indépendante parmi les radicaux méthyle et phénéthyle.
33. Composé selon la revendication 27, dans lequel R³ représente des radicaux alkyle ayant 2 à 5 atomes de carbone et R⁴ représente des radicaux méthyle, phényle et phényle substitué.
34. Composé selon la revendication 27, dans lequel R³ représente les radicaux isobutyle, n-propyle, n-butyle, isoamyle, cyclohexylméthyle, cyclohexyle, benzyle, para-fluorobenzyle, para-méthoxybenzyle, para-méthylbenzyle et 2-naphtylméthyle et R⁴ représente des radicaux phényle et phényle substitué dans lesquels les substituants du radical phényle substitué sont choisis parmi les substituants chloro, fluoro, nitro, méthoxy et amino.
35. Composé selon la revendication 27, dans lequel R³ est le cyclohexylméthyle et R⁴ est le phényle, ou R³ est l'i-amyle et R⁴ est le phényle, ou R³ est l'i-butyle et R⁴ est le phényle, ou R³ est le n-butyle et R⁴ est le phényle, ou R³ est le cyclohexyle et R⁴ est le phényle.
36. Composé selon la revendication 27, dans lequel R⁴ représente les radicaux méthyle et cyclohexyle.
37. Composé selon la revendication 27, dans lequel R et R' représentent, avec l'atome d'azote auquel ils sont rattachés, les radicaux pyrrolidinyle, pipéridinyle, morpholinyle et pipérazinyle.
38. Composé selon la revendication 27, dans lequel R³ représente des radicaux hétéroarylalkyle et R⁴ représente un méthyle ou un phényle.
39. Composé selon la revendication 1, dans lequel t = 1, x = 2, Y représente O, R⁶ représente un hydrogène et dans lequel R, R^{1'}, R^{1''}, R², R⁴ sont tels que définis dans la revendication 1 et R³ est tel que défini dans la revendication 1, l'hydrogène étant exclu, et R¹ est tel que défini dans la revendication 1, les O-alkylsérine étant exclues, et R' est tel que défini dans la revendication 1, R"SO₂ étant exclu.
40. Composé selon la revendication 39, dans lequel R' représente l'hydrogène et R représente les radicaux arylalcoxycarbonyle et hétéroaroyle.
41. Composé selon la revendication 39, dans lequel R' représente l'hydrogène et R représente les radicaux carbobenzoxy, 2-benzofurancarbonyle et 2-quinoléinyllcarbonyle.
42. Composé selon la revendication 39, dans lequel R, R^{1'} et R^{1''} représentent de façon indépendante l'hydrogène et des radicaux alkyle ayant 1 à environ 4 atomes de carbone, des radicaux alcényle, alcynyle, arylalkyle et des radicaux choisis parmi -CH₂SO₂NH₂, -CO₂CH₃, -CONHCH₃, -CON(CH₃)₂, -CH₂C(O)NHCH₃, -CH₂C(O)N(CH₃)₂, -CONH₂, -C(CH₃)₂(SCH₃), -C(CH₃)₂(S[O]CH₃) et -C(CH₃)₂(S[O]CH₃).
43. Composé selon la revendication 39, dans lequel R', R^{1'} et R^{1''} représentent de façon indépendante l'hydrogène, le méthyle, l'éthyle, le benzyle, le phénylpropyle, le propargyle, l'hydroxyle et des radicaux choisis parmi -C(O)OCH₃, -C(O)NH₂, -C(O)OH.
44. Composé selon la revendication 39, dans lequel R¹ et R^{1'} représentent tous deux l'hydrogène et R^{1''} représente -C(O)NH₂.
45. Composé selon la revendication 39, dans lequel R¹ et R^{1'} représentent tous deux l'hydrogène et R^{1''} représente le méthyle.
46. Composé selon la revendication 39, dans lequel R^{1'} représente l'hydrogène et R¹ et R^{1''} forment, considérés avec les atomes de carbone auxquels ils sont rattachés, un radical cycloalkyle à trois à six côtés.
47. Composé selon la revendication 44, dans lequel R représente un radical carbobenzoxy, 2-quinoléinyllcarbonyle et

2-benzofurancarbonyle.

48. Composé selon la revendication 39, dans lequel R³ représente des radicaux alkyle ayant de 2 à 5 atomes de carbone.

- 5 49. Composé selon la revendication 39, dans lequel R³ représente de façon indépendante des radicaux n-propyle, i-butyle, cyclohexyle, cyclohexylméthyle, i-amyle et n-butyle et R⁴ représente des radicaux phényle et phényle substitué.

- 10 50. Composé selon la revendication 39, dans lequel R³ et R⁴ représentent de façon indépendante des radicaux alkyle ayant 2 à 5 atomes de carbone, des radicaux cycloalkylalkyle, des radicaux aryle, des radicaux hétéroaryle, des radicaux arylalkyle, des radicaux hétérocycloalkylalkyle et des radicaux hétéroarylalkyle.

- 15 51. Composé selon la revendication 39, dans lequel R³ représente des radicaux benzyle, para-fluorobenzyle, para-méhoxybenzyle, para-méthylbenzyle et 2-naphtylméthyle et R⁴ représente des radicaux phényle et phényle substitués, les substituants du radical phényle substitué étant choisis parmi les substituants chloro, fluoro, nitro, méthoxy et amino.

- 20 52. Composé selon la revendication 2, 27 ou 39, dans lequel R² représente des radicaux alkyle, cycloalkylalkyle, ces radicaux étant éventuellement substitués par des radicaux halogéno et par des radicaux représentés par les formules -OR⁹ et -SR⁹ dans lesquelles R⁹ représente l'hydrogène et un radical alkyle.

- 25 53. Composé selon la revendication 2, 27 ou 39, dans laquelle R² représente CH₃SCH₂CH₂- , iso-butyle, n-butyle, benzyle, 2-naphtylméthyle et cyclohexylméthyle.

- 25 54. Composé selon la revendication 2, 27 ou 39, dans lequel R³ et R⁴ représentent de façon indépendante des radicaux alkyle, halogénoalkyle, alcényle, alcoxyalkyle, cycloalkyle, cycloalkylalkyle, hétérocycloalkyle, hétérocycloalkylalkyle, hétéroaryle, aryle, arylalkyle et hétéroarylalkyle.

- 30 55. Composé selon la revendication 2, 27 ou 39, dans lequel R³ représente des radicaux alkyle et alcényle et R⁴ représente des radicaux aryle.

- 35 56. Composition pharmaceutique comprenant un composé selon une quelconque des revendications 1, 2, 27 ou 39 et un support pharmaceutiquement acceptable.

57. Utilisation d'une composition selon la revendication 56, pour la préparation d'un médicament pour l'inhibition d'une protéase de rétrovirus.

- 40 58. Utilisation selon la revendication 57, dans laquelle la protéase de rétrovirus est une protéase de VIH.

59. Utilisation d'une composition selon la revendication 56, pour la préparation d'un médicament pour le traitement d'une infection par un rétrovirus.

- 45 60. Utilisation selon la revendication 59, dans laquelle l'infection par un rétrovirus est une infection par un VIH.

61. Utilisation d'une composition selon la revendication 56, pour la préparation d'un médicament pour le traitement du SIDA.

- 50 62. Composé selon la revendication 1, qui est :

le [2R-hydroxy-3-[(3-méthylbutyl)(méthylsulfonyl)amino]-1S-(phényleméthyl)propyl]carbamate de phényleméthyle ;

le [2R-hydroxy-3-[(3-méthylbutyl)(phénylsulfonyl)amino]-1S-(phényleméthyl)propyl]carbamate de phényleméthyle;

le N1-[2R-hydroxy-3-[(3-méthylbutyl)(méthylsulfonyl)amino]-1S-(phényleméthyl)propyl]-2S-[(2-quinoléinylcarbonyl)amino]butanediamide;

le N1-[2R-hydroxy-3-[(3-méthylbutyl)(méthylsulfonyl)amino]-1S-(phényleméthyl)propyl]-2S-[(phényleméthoxycarbonyl)amino]butanediamide;

le N1-[2R-hydroxy-3-[(3-méthylbutyl)(phénylsulfonyl)amino]-1S-(phénylméthyl)propyl]-2S-[(2-quinoléinylcarbonyl)amino]butanediamide;

le N1-[2R-hydroxy-3-[(3-méthylbutyl)(phénylsulfonyl)amino]-1S-(phénylméthyl)propyl]-2S-[(phénylméthylloxycarbonyl)amino]butanediamide;

5 le 2S-[[diméthylamino]acétyl]amino]-N-[2R-hydroxy-3-[(3-méthylbutyl)(phénylsulfonyl)amino]-1S-(phénylméthyl)propyl]-3,3-diméthylbutanamide;

le 2S-[[méthylamino]acétyl]amino]-N-[2R-hydroxy-3-[(3-méthylbutyl)(phénylsulfonyl)amino]-1S-(phénylméthyl)propyl]-3,3-diméthylbutanamide ; ou

10 le N1-[2R-hydroxy-3-[(3-méthylbutyl)(phénylsulfonyl)amino]-N4-méthyl-1S-(phénylméthyl)propyl]-2S-[(2-quinoléinylcarbonyl)amino]butanediamide ; ou

le [3-[[2-hydroxy-3-[(3-méthylbutyl)phénylsulfonyl]amino]-1-(phénylméthyl)propyl]amino]-2-méthyl-3-oxopropyl]carbamate de (4-méthoxyphényl)méthyle, [1S-[1R*(S*),2S*]].

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